Jan Delaval

Access DB# 14[illegible]

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Sabiha Rozz Examiner #: 74141 Date: 12/16/04
Art Unit: 1616 Phone Number 30 20622 Serial Number: 10/214,153
Mail Box and Bldg/Room Location: 4C70, Rm 4A45 Results Format Preferred (circle): (PAPER) DISK E-MAIL
If more than one search is submitted, please prioritize searches in order of need. ME'

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

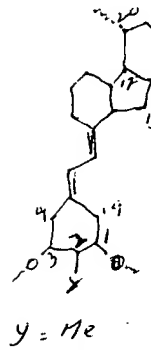
Title of Invention: Vitamin D_3 derivatives & its Production method

Inventors (please provide full names): Hiroaki TAKAYAMA et-al

Earliest Priority Filing Date: 4/30/1998 371 of PCT/JP98/01979.

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search for the compds of Cl 3 and method of making as in Cl 4.



Y = Me, Et, Alkyl.

Please search for any configuration at 1, 2, 3 & 20 positions

At 2-position methyl, ethyl or alkyl.

At 1-position - OH + OH protected as in Cl 4 (Cl 1)

At 3 - " - OH + OH protected as in Cl 4 (Cl 1)

No 19-Nor Vit. D Compds.

Please note the priority. Assignee search may also be considered

****

STAFF USE ONLY

Searcher: Jan

Searcher Phone #: 22504

Searcher Location: _____

Date Searcher Picked Up: 12/19

Date Completed: 12/19

Searcher Prep & Review Time: _____

Clerical Prep Time: 15

Online Time: + 40

Type of Search

NA Sequence (#) _____

AA Sequence (#) _____

Structure (#) ✓

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN ✓

Dialog _____

Questel/Orbit _____

Dr.Link _____

Lexis/Nexis _____

Sequence Systems _____

WWW/Internet _____

Other (specify) _____

PTO-1590 (8-01)

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=> fil casreact
FILE 'CASREACT' ENTERED AT 11:10:45 ON 19 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

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FILE CONTENT:1840 - 19 Dec 2004 VOL 141 ISS 25

**************************************************************
*                                                            *
*     CASREACT now has more than  8 million reactions        *
*                                                            *
**************************************************************

Some CASREACT records are derived from the ZIC/VINITI database (1974-1991)
provided by InfoChem, INPI data prior to 1986, and Biotransformations
database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d sta que l19
L17             STR
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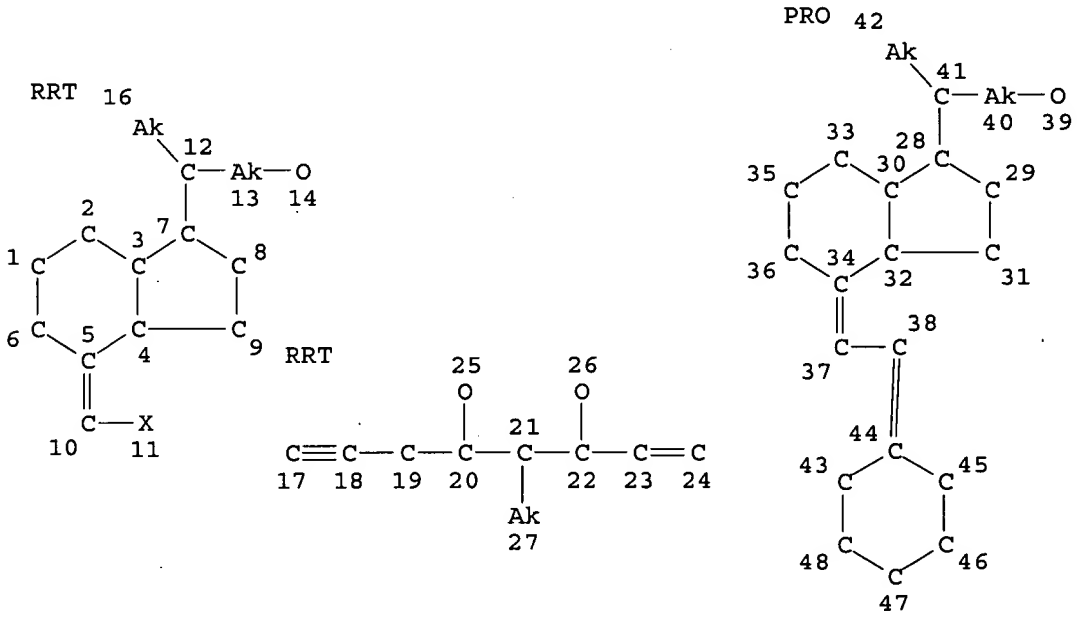


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  47

STEREO ATTRIBUTES: NONE
L19           8 SEA FILE=CASREACT SSS FUL L17 (   134 REACTIONS)

100.0% DONE    385 VERIFIED     134 HIT RXNS                  8 DOCS
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SEARCH TIME: 00.00.01

=> d his l19-

(FILE 'CASREACT' ENTERED AT 11:03:46 ON 19 DEC 2004)
L19 8 S L17 FUL
SAV L19 QAZI214/A
L20 1 S L19 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L21 8 S L19 AND (TEIJIN?/PA,CS OR (TAKAYAMA ? OR KONNO ? OR FUJISHIMA
L22 1 S L20 AND L21
L23 7 S L21 NOT L22

FILE 'CASREACT' ENTERED AT 11:10:45 ON 19 DEC 2004

=> d l22 bib abs fhit retable

L22 ANSWER 1 OF 1 CASREACT COPYRIGHT 2004 ACS on STN
AN 129:343629 CASREACT
TI Preparation of vitamin D3 derivatives and their pharmaceutical uses
IN **Takayama, Hiroaki; Konno, Katsuhiro; Fujishima, Toshie**
PA **Teijin Ltd., Japan**
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9850353	A1	19981112	WO 1998-JP1979	19980430
	W: JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 957088	A1	19991117	EP 1998-917742	19980430
	EP 957088	B1	20021218		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	AT 229937	E	20030115	AT 1998-917742	19980430
PRAI	JP 1997-114695	19970502			
	WO 1998-JP1979	19980430			

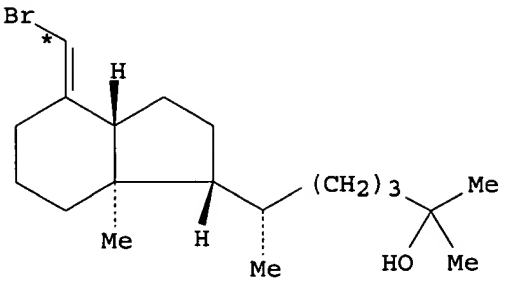
OS MARPAT 129:343629
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

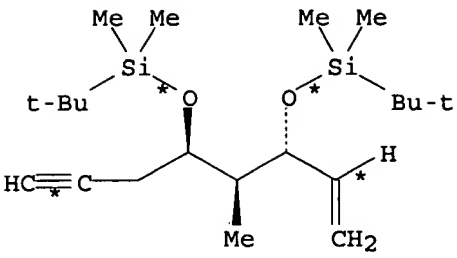
AB 1,25-Dihydroxy-2-Me vitamin D3 derivs. I [R1, R2 = H, tri(C1-7alkyl)silyl; the asym. carbon atoms at the 1-, 2- and 3-positions each independently has an α- or β-configuration], useful as remedies for osteoporosis, rachitis, accessory thyroidal hyperenergia, etc., are prepared via reaction of II (X = bromo, iodo) with III (R3, R4 = H, trihydrocarbylsilyl) in the presence of a palladium catalyst optionally followed by deprotection (removal of silyl groups). Thus, II (X = Br) was reacted with III (R3 = R4 = TBS) in toluene containing Et3N, Pd2(dba)3.CHCl3, and Ph3P at 120° to give IV (R = TBS), which was treated with camphor-10-sulfonic acid in methanol to give 63% IV (R = H). In a study using 1α,25-dihydroxyvitamin D3 receptors in the bovine thymus gland, this showed an affinity of 160 compared with 100 for

1α,25-dihydroxyvitamin D3.

RX(1) OF 1 **A** + **B** ===> **C**

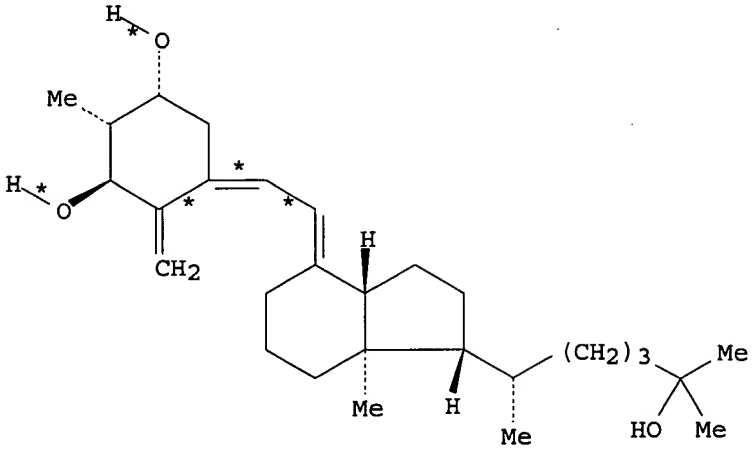


A



B

(1)



C

RX(1) RCT A **214351-89-0**, B **203126-90-3**
RGT D 121-44-8 Et3N, E 603-35-0 PPh3
PRO C **214351-93-6**
CAT 52522-40-4 Pd complex
SOL 108-88-3 PhMe

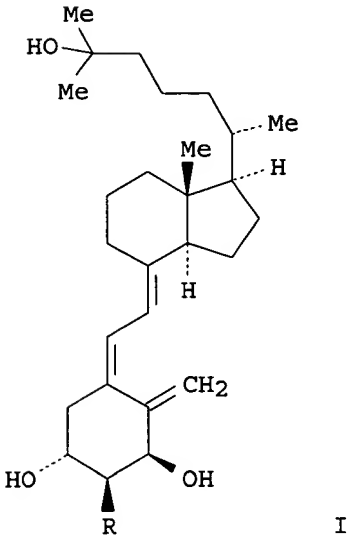
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Chugai Pharmaceutical C	1994			JP 06-41059 A	CAPLUS
Nayeri, S	1996	62	325	J Cell Biochem	CAPLUS

=> d l23 bib abs fhit retable tot

L23 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 139:396104 CASREACT
TI Concise synthesis and biological activities of 2α-Alkyl- and 2α-(ω-Hydroxyalkyl)-20-epi-1α,25-dihydroxyvitamin D3
AU Honzawa, Shinobu; Suhara, Yoshitomo; Nihei, Ken-ichi; Saito, Nozomi;

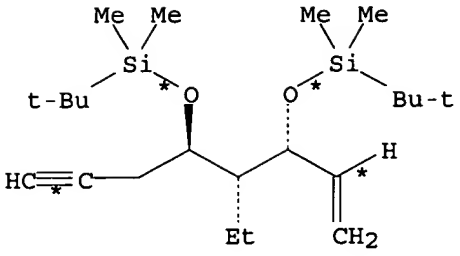
Kishimoto, Seishi; **Fujishima, Toshie**; Kurihara, Masaaki; Sugiura, Takayuki; Waku, Keizo; **Takayama, Hiroaki**; Kittaka, Atsushi
CS Faculty of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Teikyo University, Sagamiko, Kanagawa, 199-0195, Japan
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(20), 3503-3506
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science B.V.
DT Journal
LA English
GI



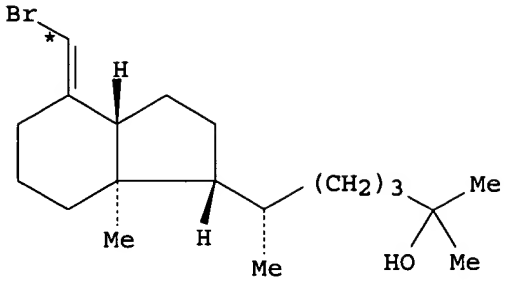
I

AB A concise route to the Trost A-ring precursor enyne for synthesizing 2α-alkylated 1α,25-dihydroxyvitamin D3 from D-glucose is presented. The enynes were coupled with the 20-epi-CD ring part to study the effect of the double modification of 2α-substitution and 20-epimerization upon biol. activity. The three novel analogs of 2α-alkyl- and four analogs of 2α-(ω-hydroxyalkyl)-20-epi-1α,25-dihydroxyvitamin D3 (I, R = Et, n-prop, Bu, CH2OH, CH2CH2OH, CH2CH2CH2OH, CH2CH2CH2CH2OH) showed higher binding affinity for vitamin D receptor (VDR) and more potent activity in induction of HL-60 cell differentiation than those of the natural hormone.

RX(3) OF 86 ...**G** + **H** ===> **I**

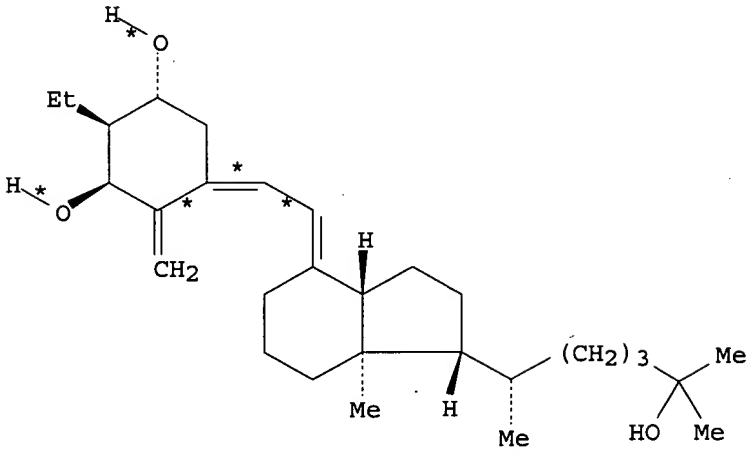


G



H

(3)



I
YIELD 56%

RX(3) RCT G **626200-66-6**, H **214351-89-0**

STAGE(1)
RGT J 121-44-8 Et3N
CAT 14221-01-3 Pd(PPh3)4
SOL 108-88-3 PhMe

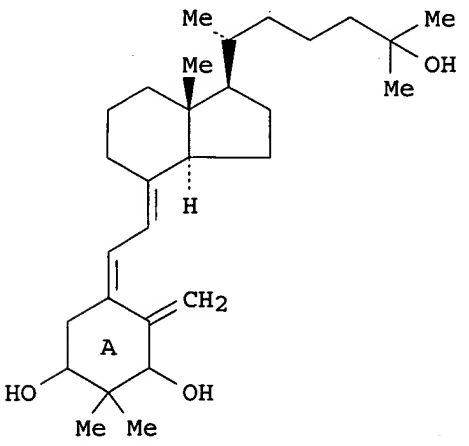
STAGE(2)
RGT K 429-41-4 Bu4N.F
SOL 109-99-9 THF
PRO I **626200-73-5**
NTE stereoselective

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1993	3	1775	Bioorg Med Chem Lett	
Binderup, L	1991	42	1569	Biochem Pharmacol	CAPLUS
Bouillon, R	1995	16	200	Endocr Rev	CAPLUS
Collins, S	1979	149	969	J Exp Med	MEDLINE

DeLuca, H	1988	2	224	FASEB J	CAPLUS
Dilworth, F	1994	47	987	Biochem Pharmacol	CAPLUS
Fujishima, T	2000	8	123	Bioorg Med Chem	CAPLUS
Fujishima, T	2001	9	525	Bioorg Med Chem	CAPLUS
Fujishima, T	1998	8	2145	Bioorg Med Chem Lett	CAPLUS
Honzawa, S				Heterocycles, in pre	
Imae, Y	1994	1213	302	Biochim Biophys Acta	CAPLUS
Jones, G	1993	4	297	Trends Endocrinol Me	
Kittaka, A	2000	2	2619	Org Lett	CAPLUS
Konno, K	1998	8	151	Bioorg Med Chem Lett	CAPLUS
Konno, K	2000	43	4247	J Med Chem	CAPLUS
Kubodera, N	1997		1071	Vitamin D	CAPLUS
Masuno, H	2002	45	1825	J Med Chem	CAPLUS
Nakagawa, K	2000	59	691	Biochem Pharmacol	CAPLUS
Okano, T	2000	7	173	Chem Biol	CAPLUS
Suhara, Y	2000	10	1129	Bioorg Med Chem Lett	CAPLUS
Suhara, Y	2001	66	8760	J Org Chem	CAPLUS
Takayama, H	2003	164	289	Vitamin D Analogs in	CAPLUS
Tocchini-Valentini, G	2001	98	5491	Proc Natl Acad Sci U	CAPLUS
Trost, B	1992	114	9836	J Am Chem Soc	CAPLUS
Wiggins, L	1963	2	188	Methods Carbohydr Ch	

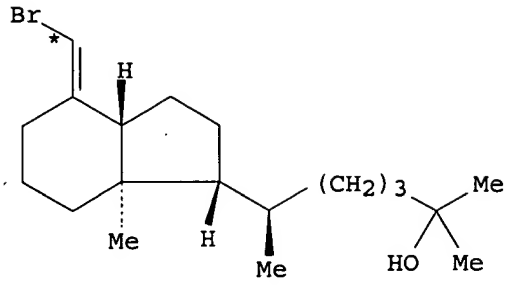
L23 ANSWER 2 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 139:323694 CASREACT
TI Synthesis of 2,2-dimethyl-1,25-dihydroxyvitamin D3: A-ring structural motif that modulates interactions of vitamin D receptor with transcriptional coactivators
AU **Fujishima, Toshie**; Kittaka, Atsushi; Yamaoka, Kazuyoshi; Takeyama, Ken-ichi; Kato, Shigeaki; **Takayama, Hiroaki**
CS Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, 199-0195, Japan
SO Organic & Biomolecular Chemistry (2003), 1(11), 1863-1869
CODEN: OBCRAK; ISSN: 1477-0520
PB Royal Society of Chemistry
DT Journal
LA English
GI



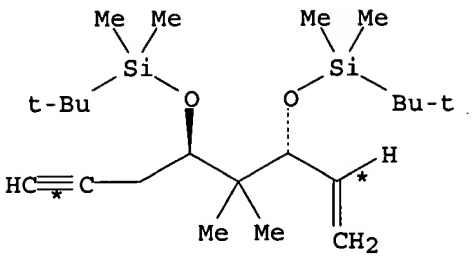
I

AB A concise synthesis of all four possible A-ring stereoisomers of 2,2-dimethyl-1,25-dihydroxyvitamin D3 (I) and characterization of their distinct transcriptional features, which appear to have been inherited from the corresponding 2α-Me derivs., is reported.

RX(12) OF 230 ...2 **AK** + 2 **AE** ===> **AL** + AM...

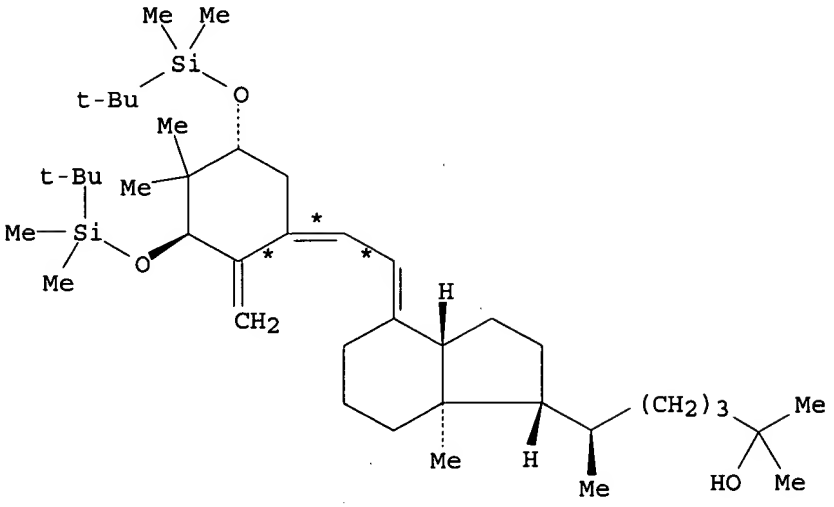


2 AK

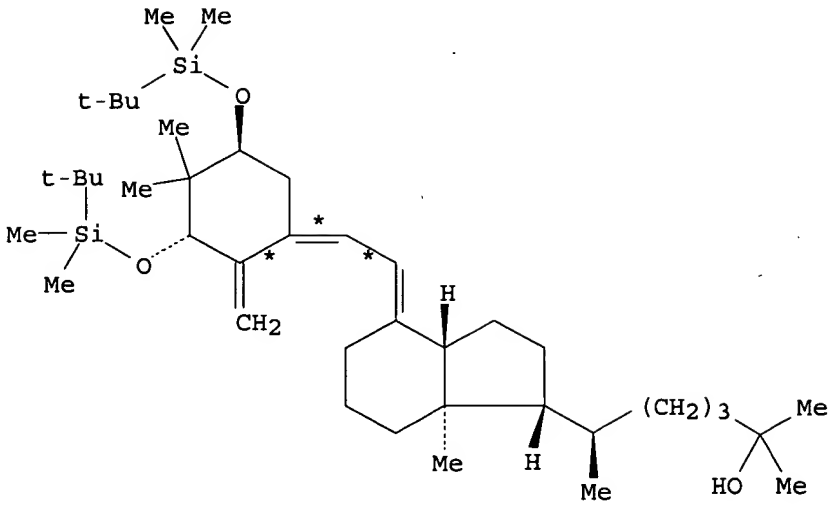


2 AE

(12)



AL



AM

RX(12) RCT AK **143705-63-9**

STAGE(1)
RGT AN 121-44-8 Et3N
CAT 14221-01-3 Pd(PPh3)4
SOL 108-88-3 PhMe

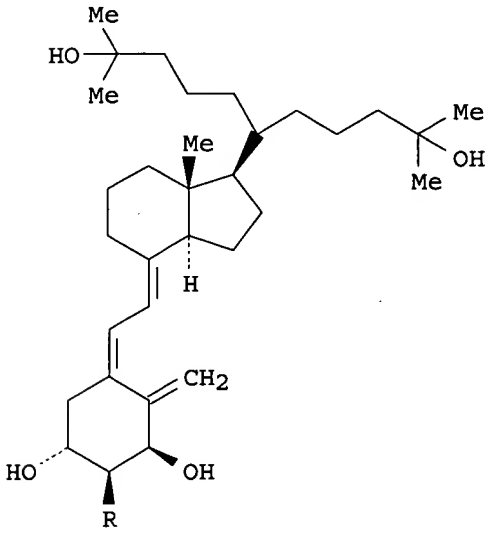
STAGE(2)
RCT AE **558437-69-7**
SOL 108-88-3 PhMe
PRO AL **613244-40-9**, AM 613244-41-0
NTE 66% overall yield, stereoselective

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1999			Vitamin D: Physiolog	
Bischof, M	1998	241	194	Exp Cell Res	CAPLUS
Bouillon, R	1995	16	200	Endocr Rev	CAPLUS
Dai, H	1994		1383	Synthesis	CAPLUS
Ettinger, R	1996	28	269	Adv Drug Res	CAPLUS
Evans, R	1988	240	889	Science	CAPLUS
Fujishima, T	2000	8	123	Bioorg Med Chem	CAPLUS
Fujishima, T	2001	9	525	Bioorg Med Chem	CAPLUS
Fujishima, T	1998	8	2145	Bioorg, Med Chem Let	CAPLUS
Fujishima, T	2001	8	1011	Chem Biol	CAPLUS
Fujishima, T	2000		93	Proceedings of the 1	
Hoph, H	1990	VII	485	Organic Synthesis Co	
Kittaka, A	2000	2	2619	Org Lett	CAPLUS
Kodera, Y	2000	275	33201	J Biol Chem	CAPLUS
Konno, K	1998	8	151	Bioorg, Med Chem Let	CAPLUS
Konno, K	2002	14	72	Chirality	CAPLUS
Konno, K	2000	43	4247	J Med Chem	CAPLUS
Muralidoharan, K	1993	58	1895	J Org Chem	
Nakagawa, K	2000	60	1937	Biochem Pharmacol	CAPLUS
Nakagawa, K	2000	59	691	Biochem Pharmacol	CAPLUS
Norman, A	1993	268	20022	J Biol Chem	CAPLUS
Rochel, N	2000	5	173	Mol Cell	CAPLUS
Rychnovsky, S	1993	58	3511	J Org Chem	CAPLUS

Rychnovsky, S	1993	58	3511	J Org Chem	CAPLUS
Rychnovsky, S	1990	31	945	Tetrahedron Lett	CAPLUS
Suhara, Y	2000	10	66	Bioorg Med Chem Lett	
Suhara, Y	2001	66	8760	J Org Chem	CAPLUS
Takeyama, K	1999	19	1049	Mol Cell Biol	CAPLUS
Tocchini-Valentini, G	2001	98	5491	Proc Natl Acad Sci U	CAPLUS
Trost, B	1992	114	1924	J Am Chem Soc	CAPLUS
Trost, B	1992	114	9836	J Am Chem Soc	CAPLUS
Vaisanen, S	2002	315	229	J Mol Biol	
Xu, H	2002	415	813	Nature	CAPLUS
Zhu, G	1995	95	1877	Chem Rev	CAPLUS

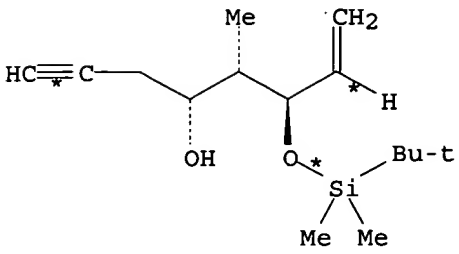
L23 ANSWER 3 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 138:39458 CASREACT
TI Synthesis and testing of 2α-Modified 1α,25-Dihydroxyvitamin D3 analogues with a double side chain: marked cell differentiation activity
AU Suhara, Yoshitomo; Kittaka, Atsushi; Kishimoto, Seishi; Calverley, Martin J.; **Fujishima, Toshie**; Saito, Nozomi; Sugiura, Takayuki; Waku, Keizo; **Takayama, Hiroaki**
CS Faculty of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Teikyo University, Sagamiko, Kanagawa, 199-0195, Japan
SO Bioorganic & Medicinal Chemistry Letters (2002), 12(22), 3255-3258
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
GI



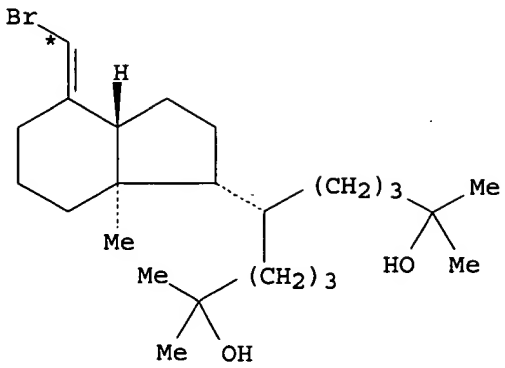
I

AB The 2α-methyl-, 2α-(3-hydroxypropyl)-, and 2α-(3-hydroxypropoxy)-derivs. of the double side chain analog of 1α,25-dihydroxyvitamin D3, I (R = Me, (CH2)3OH, O(CH2)3OH) were synthesized using Trost A-ring/CD-ring connective strategy. Regarding the requisite A-ring building blocks, a new, high yield and stereoselective route to the 2α-Me compound was developed. All three new analogs showed potent HL-60 cancer cell differentiation activity.

RX(9) OF 59 ...**AD** + **AF** ===> **AG**



AD



AF

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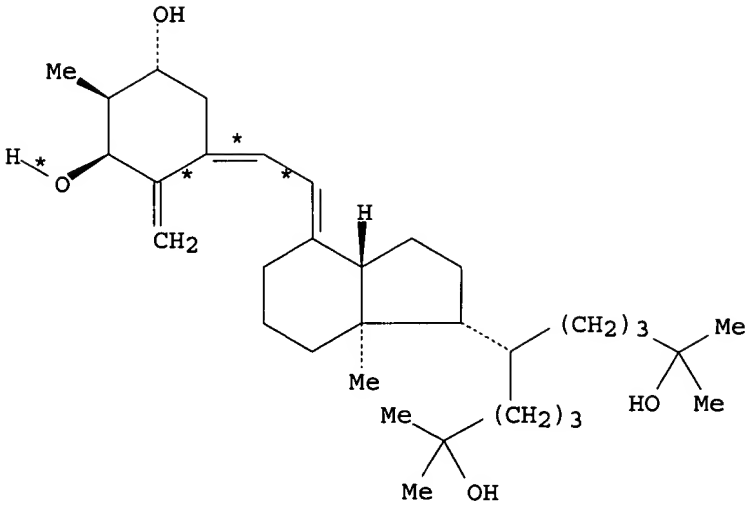


AG
YIELD 12%

RX(9) RCT AD **478944-13-7**, AF **478944-14-8**

STAGE(1)
CAT 14221-01-3 Pd(PPh3)4
SOL 121-44-8 Et3N, 108-88-3 PhMe

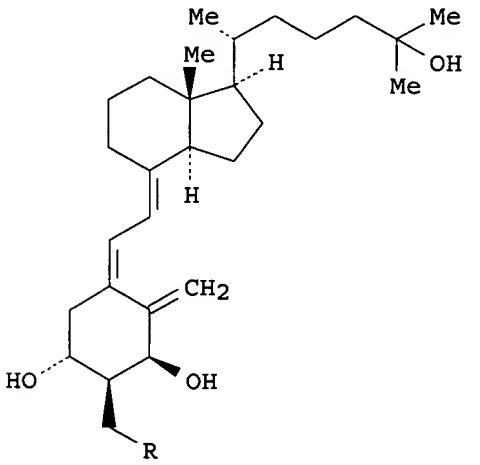
STAGE(2)
RGT AH 429-41-4 Bu4N.F
SOL 109-99-9 THF
PRO AG **478944-08-0**
NTE stereoselective

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Anon	1997			Vitamin D	
Binderup, L	1991	42	1569	Biochem Pharmacol	CAPLUS
Collins, S	1979	149	969	J Exp Med	MEDLINE
Ettinger, R	1996	28	269	Adv Drug Res	CAPLUS
Fujishima, T	1998	8	2145	Bioorg Med Chem Lett	CAPLUS
Imae, Y	1994	1213	302	Biochim Biophys Acta	CAPLUS
Kittaka, A	2000	2	2619	Org Lett	CAPLUS
Konno, K	1998	8	151	Bioorg Med Chem Lett	CAPLUS
Konno, K	2000	43	4247	J Med Chem	CAPLUS
Kurek-Tyrlik, A	1997		30	Vitamin D: Chemistry	
Norman, A	2000	43	2719	J Med Chem	CAPLUS
Pougny, J	1982		0186	J Chem Res, Miniprin	
Suhara, Y	2001	75	197	53th Meeting of the	
Suhara, Y	2000	10	1129	Bioorg Med Chem Lett	CAPLUS
Suhara, Y	2001	66	6760	J Org Chem	
Takeyama, K	1999	19	1049	Mol Cell Biol	CAPLUS
Trost, B	1992	114	9836	J Am Chem Soc	CAPLUS
Umezono, K	1991	65	1255	Cell	
Uskokovic, M	1997		19	Vitamin D: Chemistry	
Wiggins, L	1963	2	188	Methods Carbohydr Ch	

L23 ANSWER 4 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 136:134951 CASREACT
TI Efficient and Versatile Synthesis of Novel 2α-Substituted 1α,25-Dihydroxyvitamin D3 Analogues and Their Docking to Vitamin D Receptors
AU Suhara, Yoshitomo; Nihei, Ken-ichi; Kurihara, Masaaki; Kittaka, Atsushi; Yamaguchi, Kentaro; **Fujishima, Toshie**; **Konno, Katsuhiro**; Miyata, Naoki; **Takayama, Hiroaki**
CS Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa, 199-0195, Japan
SO Journal of Organic Chemistry (2001), 66(26), 8760-8771
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
GI

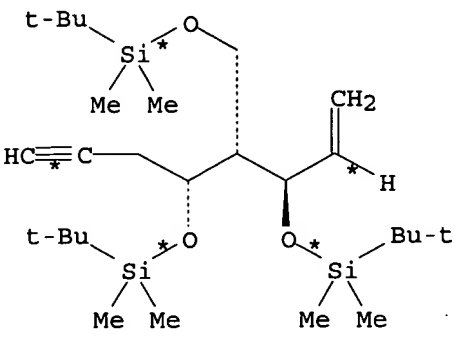


I

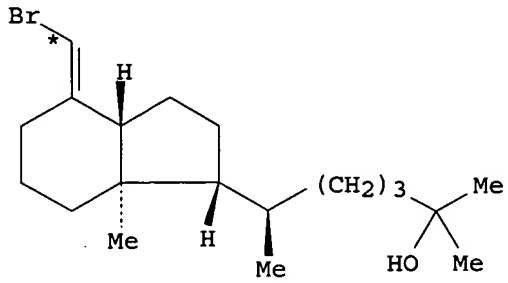
AB Novel 2α-substituted 1α,25-dihydroxyvitamin D3 analogs I [R =

OH, CH2OH, (CH2)2OH, (CH2)3OH, Me, CH2Me, (CH2)2Me] with 2α-alkyl and 2α-hydroxyalkyl groups were systematically synthesized from a D-xylose derivative Their conformation on binding to the ligand binding domain (LBD) of the vitamin D receptor was analyzed. It has been found that I [R = (CH2)3OH] best fits the cavity of the LBD, and the binding activity is three times higher than that for the natural hormone.

RX(1) OF 553 ...**A** + **B** ===> **C**

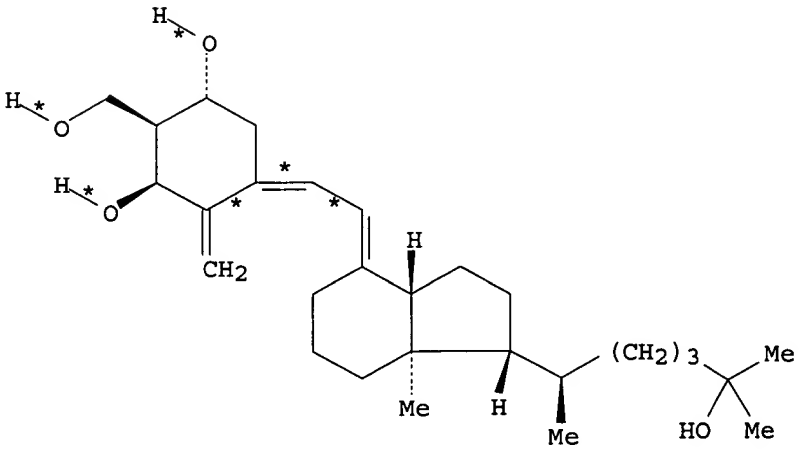


A



B

(1) →



C
YIELD 40%

RX(1) RCT A **288380-83-6**, B **143705-63-9**

STAGE(1)
RGT D 121-44-8 Et3N
CAT 52522-40-4 Pd complex, 603-35-0 PPh3
SOL 121-44-8 Et3N, 108-88-3 PhMe

STAGE(2)
RGT E 3144-16-9 10-CSA

SOL 67-56-1 MeOH
PRO C **288380-71-2**
NTE stereoselective, palladium-catalyzed coupling in first stage, deprotection in second stage

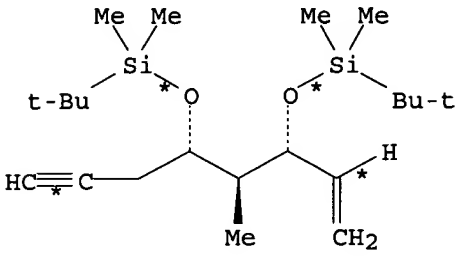
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehm, M	1999	6	265	Chem Biol	CAPLUS
Bouillon, R	1995	16	200	Endocr Rev	CAPLUS
Dai, H	1994		1383	Synthesis	CAPLUS
Deluca, H	1998	56	54	Nutr Rev	
Ettinger, R	1996	28	269	Adv Drug Res	CAPLUS
Feldman, D	1997			Vitamin D	
Fujishima, T	1998	8	2145	Bioorg Med Chem Lett	CAPLUS
Imae, Y	1994	1213	302	Biochim Biophys Acta	CAPLUS
Kittaka, A	2000	2	2619	Org Lett	CAPLUS
Konno, K	1998	8	151	Bioorg Med Chem Lett	CAPLUS
Konno, K	2000	43	4247	J Med Chem	CAPLUS
Moriety, R	1995	36	51	Tetrahedron Lett	
Okano, T	1989	163	1444	Biochem Biophys Res	CAPLUS
Ono, Y	1997	45	1626	Chem Pharm Bull	CAPLUS
Rochel, N	2000	5	173	Mol Cell	CAPLUS
Suhara, Y	2000	10	1129	Bioorg Med Chem Lett	CAPLUS
Takeyama, K	1999	19	1049	Mol Cell Biol	CAPLUS
Trost, B	1992	114	9836	J Am Chem Soc	CAPLUS
Tsugawa, N	2000	23	66	Biol Pharm Bull	CAPLUS
Umemoto, K	1991	65	1255	Cell	
Yanagisawa, J	1999	283	1317	Science	CAPLUS
Zhu, G	1995	95	1877	Chem Rev	CAPLUS

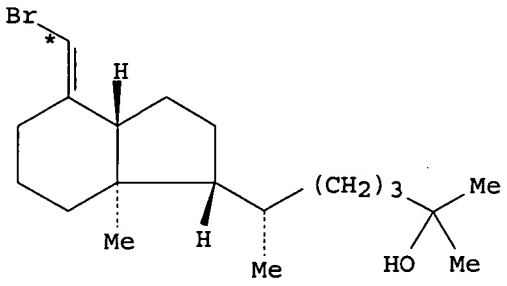
L23 ANSWER 5 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 134:353446 CASREACT
TI Systematic studies on synthesis, structural elucidation, and biological evaluation of A-ring diastereomers of 2-methyl-1α,25-dihydroxyvitamin D3 and 20-epi-2-methyl-1α,25-dihydroxyvitamin D3
AU **Takayama, H.; Konno, K.; Fujishima, T.;** Maki, S.; Liu, Z.; Miura, D.; Chokki, M.; Ishizuka, S.; Smith, C.; DeLuca, H. F.; Nakagawa, K.; Kurobe, M.; Okano, T.
CS Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa, 199-0195, Japan
SO Steroids (2001), 66(3-5), 277-285
CODEN: STEDAM; ISSN: 0039-128X
PB Elsevier Science Inc.
DT Journal
LA English
AB All possible A-ring diastereomers of 2-methyl-1α,25-dihydroxyvitamin D3 and 20-epi-2-methyl-1α,25-dihydroxyvitamin D3 were synthesized by palladium-catalyzed coupling reaction of A-ring 'enyne' synthons with CD-ring portions. The A-ring synthons were rationally synthesized via a novel and practical route, starting with Me (R)-(+)- and (S)-(-)-3-hydroxy-2-methyl-propionate, in good yields. X-ray crystallog. anal. of 2α-methyl-1α,25-dihydroxyvitamin D3 (I) and conformational anal. of the A-ring of 2α-methyl- and 2β-methyl-1α,25-dihydroxyvitamin D3 were carried out, and the results are described. All A-ring diastereomers, thus synthesized, were biol. evaluated both in vitro and in vivo. The biol. potency was highly dependent on the stereochem. of the A-ring substituents. In particular, I showed 4-fold higher vitamin D receptor [VDR] binding activity than the natural hormone, and its 20-epimer exhibited exceptionally high activity, 12-fold more potent in VDR binding, 7-fold in calcium mobilization, and 590-fold in induction of human promyelocytic leukemia (HL-60) cell

differentiation as compared with the natural hormone. Further, the 20-epi-2β-Me-1β,3α(OH)2 isomer had significant biol. potencies compared to the natural hormone despite having 1β-OH configuration. The transcriptional activities on human osteocalcin gene promoter, including VDRE in transfected mammalian cells, were also evaluated. Finally, there was a clear contrast between the effects of the 2-Me group on the HL-60 cell differentiation- and apoptosis-inducing activities.

RX(16) OF 106 ...**AK** + **AR** ===> **AS**

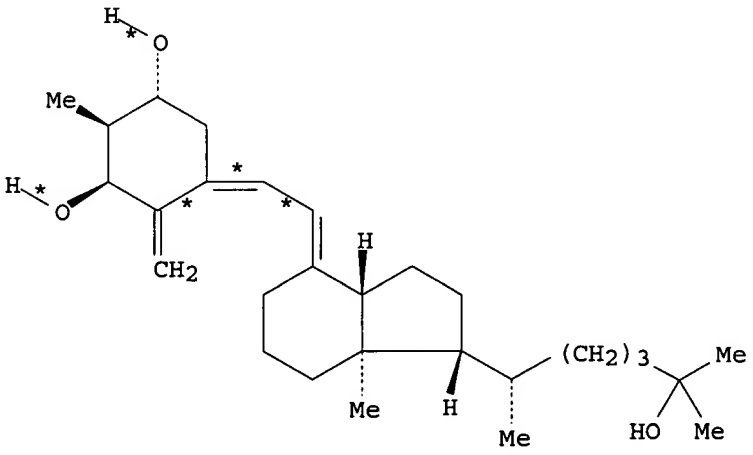


AK



AR

(16)



AS

RX(16) RCT AK **215394-23-3**, AR **214351-89-0**

STAGE(1)
RGT AT 121-44-8 Et3N
CAT 51364-51-3 Ph2-pentadienone Pd, 603-35-0 PPh3
SOL 108-88-3 PhMe

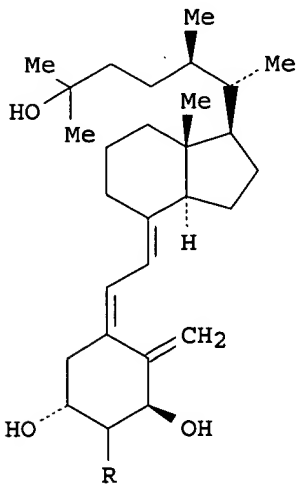
STAGE(2)
RGT AU 3144-16-9 10-CSA
SOL 67-56-1 MeOH

PRO AS **214351-84-5**

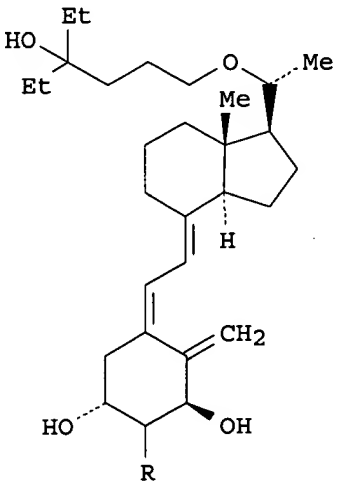
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anet, F	1962	84	1053	J Am Chem Soc	CAPLUS
Bouillon, R	1995	16	200	Endocri Rev	CAPLUS
Ettinger, R	1996	28	269	Adv Drug Res	CAPLUS
Fujishima, T	1998	8	2145	Bioorg Med Chem Lett	CAPLUS
Konno, K	1998	8	151	Bioorg Med Chem Lett	CAPLUS
Muralidharan, K	1993	58	1895	J Org Chem	CAPLUS
Nakagawa, K	2000	59	691	Biochem Pharmacol	CAPLUS
Nakagawa, K				Biochem Pharmacol in	
Nishii, Y	1991		289	Vitamin D	CAPLUS
Ohtani, I	1991	13	4092	J Am Chem Soc	
Okamura, W	1974	71	4194	Proc Natl Acad Sci U	CAPLUS
Okamura, W	1997		937	Vitamin D	
Perlman, K	1990	31	1823	Tetrahedron Lett	CAPLUS
Posner, G	1992	35	3280	J Med Chem	CAPLUS
Pychnovsky, S	1993	58	3511	J Org Chem	
Scinski, R	1998	41	4662	J Med Chem	
Suwin'ska, K	1996	B52	550	Acta Cryst	CAPLUS
Trost, B	1992		9836	J Am Chem Soc	CAPLUS
Wing, R	1975	97	4980	J Am Chem Soc	CAPLUS

L23 ANSWER 6 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 134:340606 CASREACT
TI Highly potent cell differentiation-inducing analogues of 1α,25-dihydroxyvitamin D3: synthesis and biological activity of 2-methyl-1,25-dihydroxyvitamin D3 with side-chain modifications
AU **Fujishima, T.**; Zhaopeng, L.; **Konno, K.**; Nakagawa, K.; Okano, T.; Yamaguchi, K.; **Takayama, H.**
CS Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa, 199-0195, Japan
SO Bioorganic & Medicinal Chemistry (2001), 9(2), 525-535
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
GI



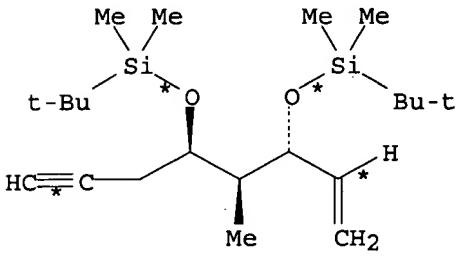
I



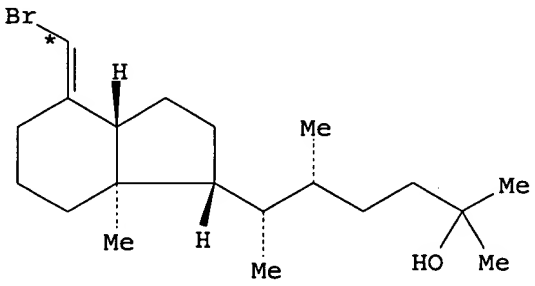
II

AB Eight 2-Me substituted analogs of 20-epi-22R-methyl-1α,25-dihydroxyvitamin D3 (I, R = H) and 20-epi-24,26,27-trihomo-22-oxa-1α,25-dihydroxyvitamin D3 (II, R = H: KH-1060) were convergently synthesized. Preparation of the CD-ring portions with modified side chains of I and II, followed by palladium-catalyzed cross-coupling with the A-ring enyne synthons (20a-d), (3S,4S,5R)-, (3S,4R,5R)-, (3S,4S,5S)- and (3R,4R,5S)-3,5-bis[(tert-butyldimethylsilyl)oxy]-4-methyloct-1-en-7-yne, afforded two sets of four A-ring stereoisomers of 20-epi-2,22-dimethyl-1,25-dihydroxyvitamin D3 (I, R = Me) and 20-epi-24,26,27-trihomo-2-methyl-22-oxa-1,25-dihydroxyvitamin D3 (II, R = Me). The biol. profiles of the hybrid analogs were assessed in terms of affinity for vitamin D receptor (VDR) and HL-60 cell differentiation-inducing activity in comparison with the natural hormone. The combined modifications of the A-ring at the 2-position and the side chain yielded analogs with high potency.

RX(1) OF 82 ...**A** + **B** ===> **C**

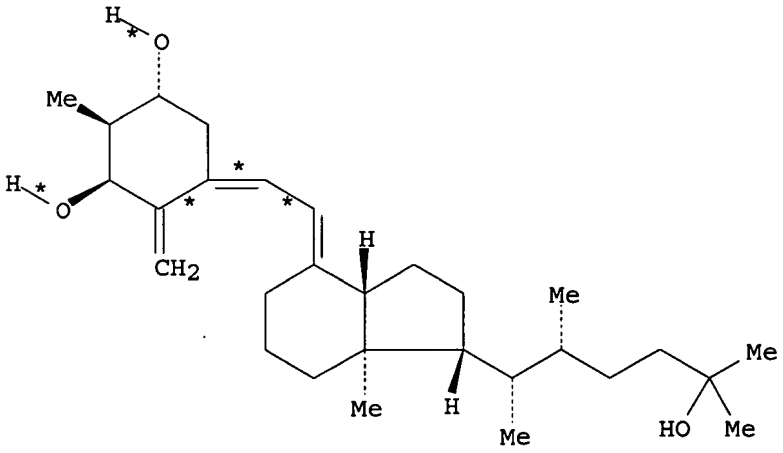


A



B

(1) →



C

RX(1) RCT A **203126-90-3**, B **305371-77-1**

STAGE(1)
RGT D 121-44-8 Et3N
CAT 52522-40-4 Pd complex, 603-35-0 PPh3
SOL 108-88-3 PhMe

STAGE(2)

CAT 3144-16-9 10-CSA
SOL 67-56-1 MeOH
PRO C **305371-78-2**
NTE key step

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1999			Vitamin D: Physiolog	
Binderup, L	1991	42	1569	Biochem Pharmacol	CAPLUS
Bischof, M	1998	241	194	Exp Cell Res	CAPLUS
Bouillon, R	1995	16	200	Endocrine Rev	CAPLUS
Brackman, D	1995	58	547	J Leukocyt Biol	CAPLUS
Dai, H	1994		1383	Synthesis	CAPLUS
Dilworth, F	1994	47	987	Biochem Pharmacol	CAPLUS
Ettinger, R	1996	28	269	Adv Drug Res	CAPLUS
Fujishima, T	2000	8	123	Bioorg Med Chem	CAPLUS
Fujishima, T	1998	8	2145	Bioorg Med Chem Lett	CAPLUS
Imae, Y	1994	1213	302	Biochim Biophys Acta	CAPLUS
Kittaka, A	2000	2	2619	Org Lett	CAPLUS
Konno, K	1998	8	151	Bioorg Med Chem Lett	CAPLUS
Masuda, S	1997		159	Proceedings of the T	
Murayama, E	1986	57	4410	Chem Pharm Bull	
Nakagawa, K	2000	59	691	Biochem Pharmacol	CAPLUS
Posner, G	1994	4	2919	Bioorg Med Chem Lett	CAPLUS
Reddy, G	1997		139	Proceedings of the T	
Rochel, N	2000	5	173	Molecular Cell	CAPLUS
Suhara, Y	2000	10	1129	Bioorg Med Chem Lett	CAPLUS
Trost, B	1992	114	9836	J Am Chem Soc	CAPLUS
Vitale, C	1997		34	Proceedings of the T	
Wilson, S	1993	3	341	Bioorg Med Chem Lett	CAPLUS
Yamada, S	1998	41	1467	J Med Chem	CAPLUS
Yamamoto, K	1996	39	2727	J Med Chem	CAPLUS
Yamamoto, K	2000	97	1467	Proc Natl Acad Sci U	CAPLUS
Zhu, G	1995	95	1877	Chem Rev	CAPLUS

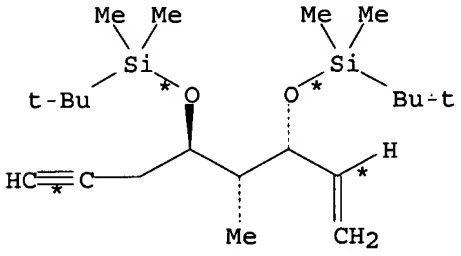
L23 ANSWER 7 OF 7 CASREACT COPYRIGHT 2004 ACS on STN
AN 134:29607 CASREACT
TI Synthesis, biological evaluation, and conformational analysis of A-ring diastereomers of 2-methyl-1,25-dihydroxyvitamin D3 and their 20-epimers: unique activity profiles depending on the stereochemistry of the A-ring and at C-20
AU **Konno, Katsuhiro**; **Fujishima, Toshie**; Maki, Shojiro; Liu, Zhaopeng; Miura, Daishiro; Chokki, Manabu; Ishizuka, Seiichi; Yamaguchi, Kentaro; Kan, Yukiko; Kurihara, Masaaki; Miyata, Naoki; Smith, Connie; DeLuca, Hector F.; **Takayama, Hiroaki**
CS Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko Kanagawa, 199-0195, Japan
SO Journal of Medicinal Chemistry (2000), 43(22), 4247-4265
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

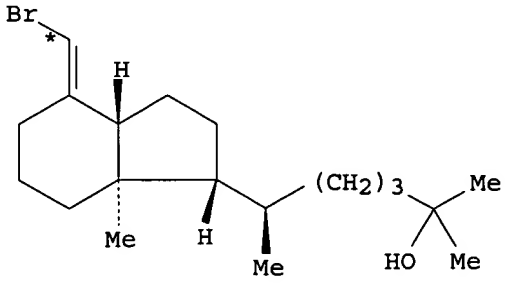
AB All eight possible A-ring diastereomers of 2-methyl-1,25-dihydroxyvitamin D3, e.g. I, and 2-methyl-20-epi-1,25-dihydroxyvitamin D3, e.g. II, were

convergently synthesized. The A-ring enyne synthons III were synthesized starting with Me (S)-(+)- or (R)-(-)-3-hydroxy-2-methylpropionate. This was converted to the alc. IV as a 1:1 epimeric mixture in several steps. After separation by column chromatog., each isomer led to the requisite A-ring enyne synthons III again as 1:1 mixts. at C-1. Coupling of the resulting A-ring enynes with the CD-ring portions in the presence of a Pd catalyst afforded the 2-Me analogs in good yield. In this way, all possible A-ring diastereomers were synthesized. The synthesized analogs were biol. evaluated both in vitro and in vivo. The potency was highly dependent on the stereochem. of each isomer. In particular, the ααβ-isomer I exhibited 4-fold higher potency than 1α,25-dihydroxyvitamin D3 both in bovine thymus VDR binding and in elevation of rat serum calcium concentration and was twice as potent as the parent compound in HL-60 cell differentiation. Furthermore, its 20-epimer, i.e., 20-epi-ααβ II, exhibited exceptionally high activities: 12-fold higher in VDR binding affinity, 7-fold higher in calcium mobilization, and 590-fold higher in HL-60 cell differentiation, as compared to 1α,25-dihydroxyvitamin D3. Accordingly, the double modification of 2-Me substitution and 20-epimerization resulted in unique activity profiles. Conformational anal. of the A-ring by 1H NMR and an X-ray crystallog. anal. of the ααβ-isomer I are also described.

RX(1) OF 97 ...**A** + **B** ===> **C**

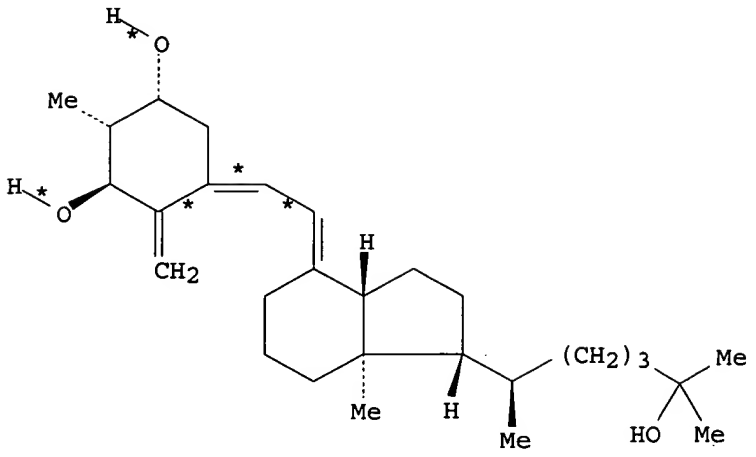


A



B

(1)



C
YIELD 41%

RX(1) RCT A **215394-12-0**, B **143705-63-9**

STAGE(1)
RGT D 121-44-8 Et3N
CAT 52522-40-4 Pd complex, 603-35-0 PPh3
SOL 108-88-3 PhMe

STAGE(2)
RGT E 3144-16-9 10-CSA
SOL 67-56-1 MeOH
PRO C **158388-11-5**
NTE KEY STEP ,STEREOSELECTIVE

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abe, J	1991	129	832	Endocrinology	CAPLUS
Ando, K	1995	43	189	Chem Pharm Bull	CAPLUS
Anet, F	1962	84	1053	J Am Chem Soc	CAPLUS
Binderup, L	1991	42	1569	Biochem Pharmacol	CAPLUS
Bishop, J	1994	8	1277	J Bone Miner Res	
Boehm, M	1999	6	265	Chem Biol	CAPLUS
Bouillon, R	1995	16	200	Endocr Rev	CAPLUS
Chen, Y	1996	37	9361	Tetrahedron Lett	CAPLUS
Collins, S	1979	149	969	J Exp Med	MEDLINE
Dai, H	1994		1383	Synthesis	CAPLUS
Darwish, H	1996	53	321	Prog Nucleic Acid Re	CAPLUS
Dilworth, F	1994	47	987	Biochem Pharmacol	CAPLUS
Eguchi, T	1990	18	19	Bioorg Chem	CAPLUS
Eguchi, T	1991	19	327	Bioorg Chem	CAPLUS
Ettinger, R	1996	28	269	Adv Drug Res	CAPLUS
Evans, R	1988	240	889	Science	CAPLUS
Fujishima, T	2000	8	123	Bioorg Med Chem	CAPLUS
Honda, A	1991	56	142	Steroids	CAPLUS
Imae, Y	1994	1213	302	Biochim Biophys Acta	CAPLUS
Inaba, M	1987	258	421	Arch Biochem Biophys	CAPLUS
Ishida, H	1995	60	1828	J Org Chem	CAPLUS
Ishizuka, S	1986	25	505	J Steroid Biochem	CAPLUS
Kabakoff, B	1982	215	582	Arch Biochem Biophys	CAPLUS
Konno, K	1998	8	151	Bioorg Med Chem Lett	CAPLUS

Konno, K	1998		2145	Bioorg Med Chem Lett	
Konno, K	1992	40	1120	Chem Pharm Bull	CAPLUS
Linclau, B	1997	7	1461	Bioorg Med Chem Lett	CAPLUS
Liu, Y	1997	272	3336	J Biol Chem	CAPLUS
Midland, M	1993	3	1799	Bioorg Med Chem Lett	CAPLUS
Miyaura, C	1981	102	937	Biochem Biophys Res	CAPLUS
Moriarty, R	1995	36	51	Tetrahedron Lett	CAPLUS
Moriarty, R	1995	36	9265	Tetrahedron Lett	CAPLUS
Muralidharan, K	1993	58	1895	J Org Chem	CAPLUS
Murayama, E	1986	34	4410	Chem Pharm Bull	CAPLUS
Nakagawa, K	2000	59	691	Biochem Pharmacol	CAPLUS
Nakagawa, K				Biochem Pharmacol, i	
Norman, A	1993	268	20022	J Biol Chem	CAPLUS
Norman, A	1999	74	323	J Cell Biochem	CAPLUS
Ohtani, I	1991	113	4092	J Am Chem Soc	CAPLUS
Okamoto, S	1982	244	E159	Am J Physiol	
Okamura, W	1992	49	10	J Cell Biochem	CAPLUS
Okamura, W	1974	71	4194	Proc Natl Acad Sci U	CAPLUS
Okamura, W	1997		939	Vitamin D	CAPLUS
Okano, T	1989	163	1444	Biochem Biophys Res	CAPLUS
Ono, Y	1997	45	1626	Chem Pharm Bull	CAPLUS
Perlman, K	1990	31	1823	Tetrahedron Lett	CAPLUS
Perlman, K	1991	32	7663	Tetrahedron Lett	CAPLUS
Pike, J	1991	11	189	Annu Rev Nutr	CAPLUS
Posner, G	1993	3	1829	Bioorg Med Chem Lett	CAPLUS
Posner, G	1994	4	2919	Bioorg Med Chem Lett	CAPLUS
Posner, G	1995	5	2163	Bioorg Med Chem Lett	CAPLUS
Posner, G	1992	35	3280	J Med Chem	CAPLUS
Posner, G	1998	41	3008	J Med Chem	CAPLUS
Posner, G	1993	58	7209	J Org Chem	CAPLUS
Posner, G	1994	59	7855	J Org Chem	CAPLUS
Posner, G	1995	60	4617	J Org Chem	CAPLUS
Posner, G	1997	62	3299	J Org Chem	CAPLUS
Rochel, N	2000	5	173	Mol Cell	CAPLUS
Rychnovsky, S	1993	58	3511	J Org Chem	CAPLUS
Rychnovsky, S	1990	31	945	Tetrahedron Lett	CAPLUS
Sabbe, K	1996	6	1697	Bioorg Med Chem Lett	CAPLUS
Schroedinger Inc				Macro Model version	
Sicinski, R	1998	41	4662	J Med Chem	CAPLUS
Suda, T	1970	100	1049	J Nutr	CAPLUS
Suhara, Y	2000	10	1129	Bioorg Med Chem Lett	CAPLUS
Suwinska, K	1996	B52	550	Acta Crystallogr	CAPLUS
Tanaka, Y	1984	229	348	Arch Biochem Biophys	CAPLUS
Tazumi, K	1994		1903	J Chem Soc, Chem Com	CAPLUS
Trost, B	1992	114	1924	J Am Chem Soc	CAPLUS
Trost, B	1992	114	9836	J Am Chem Soc	CAPLUS
Trost, B	1994	35	8119	Tetrahedron Lett	CAPLUS
Uhland-Smith, A	1993	123	1777	J Nutr	CAPLUS
Umesono, K	1991	65	1255	Cell	CAPLUS
Vrielynck, S	1995	36	9023	Tetrahedron Lett	CAPLUS
Wing, R	1975	97	4980	J Am Chem Soc	CAPLUS
Wing, R	1974	186	939	Science	CAPLUS
Wu, Y	1997	7	923	Bioorg Med Chem Lett	
Yamada, S	1979	27	3196	Chem Pharm Bull	CAPLUS
Yamada, S	1998	41	1467	J Med Chem	CAPLUS
Yamamoto, K	1995	5	979	Bioorg Med Chem Lett	CAPLUS
Yamamoto, K	1999	9	1041	Bioorg Med Chem Lett	CAPLUS
Yamamoto, K	1996	39	2727	J Med Chem	CAPLUS
Yamamoto, K	2000	97	1467	Proc Natl Acad Sci U	CAPLUS
Zhu, G	1996	6	1703	Bioorg Med Chem Lett	CAPLUS
Zhu, G	1995	95	1877	Chem Rev	CAPLUS
Zhu, G	1999	42	3539	J Med Chem	

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=> => fil reg
FILE 'REGISTRY' ENTERED AT 11:26:32 ON 19 DEC 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   17 DEC 2004  HIGHEST RN 799559-65-2
DICTIONARY FILE UPDATES:  17 DEC 2004  HIGHEST RN 799559-65-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l29
L24             STR
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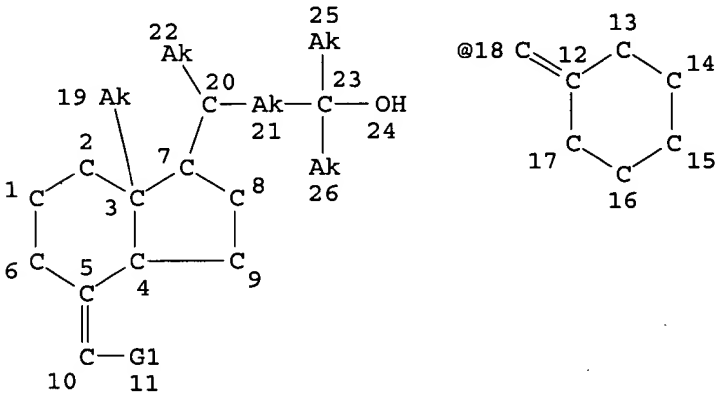


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VAR G1=X/18
NODE ATTRIBUTES:
CONNECT IS M1  RC AT  13
CONNECT IS M1  RC AT  14
CONNECT IS M1  RC AT  15
CONNECT IS M1  RC AT  16
CONNECT IS M1  RC AT  17
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   1  12
NUMBER OF NODES IS  26

STEREO ATTRIBUTES: NONE
L26         1136 SEA FILE=REGISTRY CSS FUL L24
L27              STR
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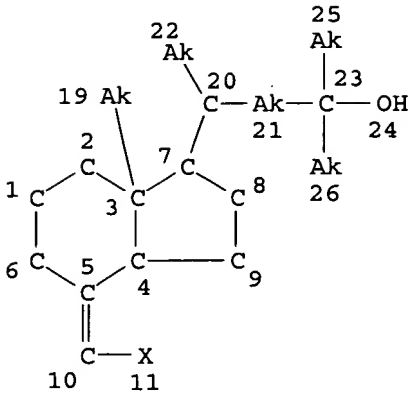


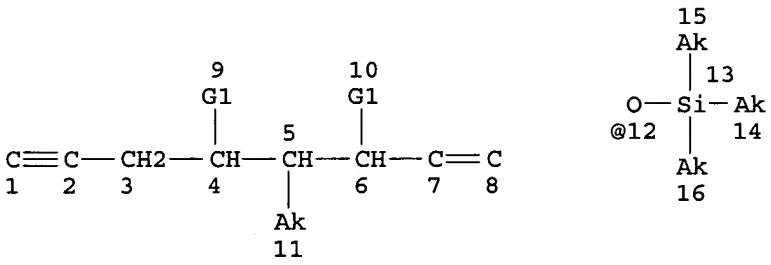
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L29 4 SEA FILE=REGISTRY SUB=L26 CSS FUL L27

100.0% PROCESSED 13 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

=> d sta que l44
L42 STR



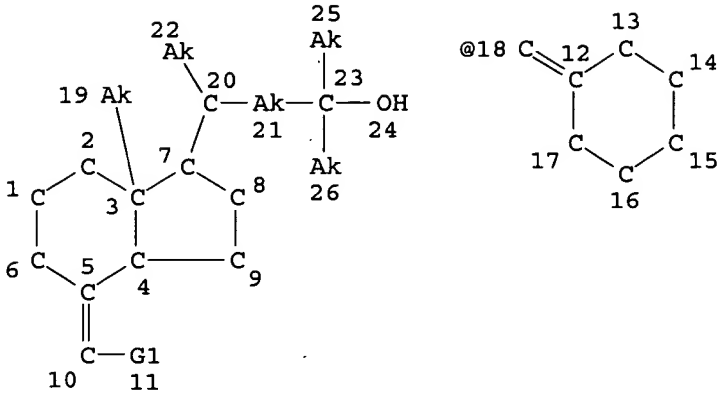
VAR G1=OH/12
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L44 23 SEA FILE=REGISTRY CSS FUL L42

100.0% PROCESSED 26505 ITERATIONS 23 ANSWERS
SEARCH TIME: 00.00.01

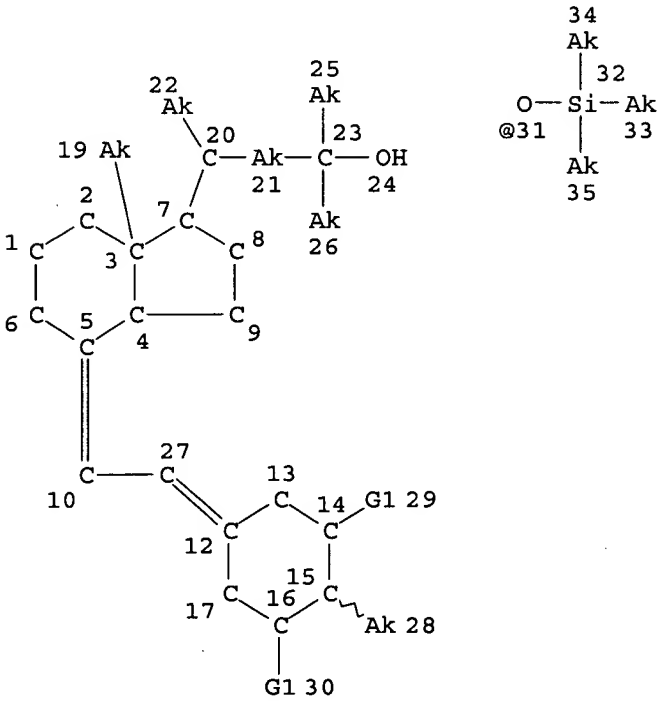
=> d sta que l39
L24 STR



VAR G1=X/18
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 13
CONNECT IS M1 RC AT 14
CONNECT IS M1 RC AT 15
CONNECT IS M1 RC AT 16
CONNECT IS M1 RC AT 17
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1 12
NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE
L26 1136 SEA FILE=REGISTRY CSS FUL L24
L30 STR

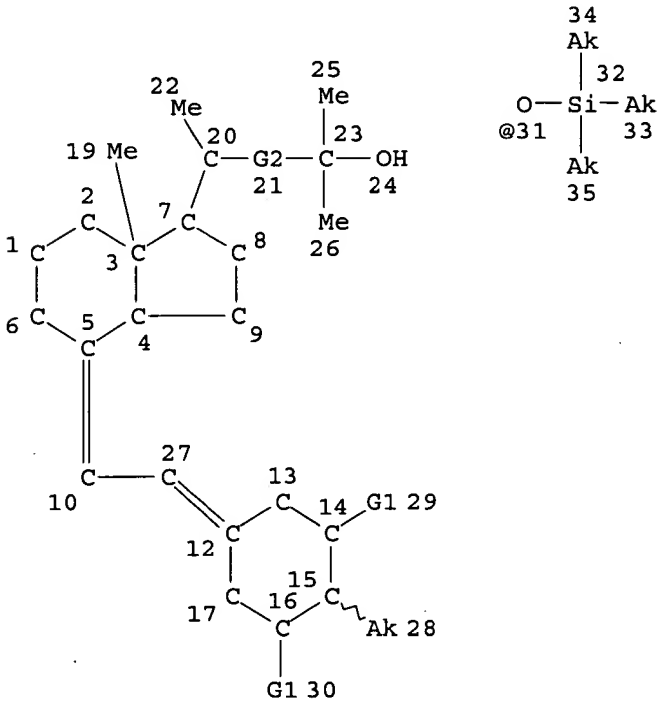


VAR G1=OH/31

NODE ATTRIBUTES:
CONNECT IS M1 RC AT 13
CONNECT IS M1 RC AT 17
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 12 5
NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE
L32 106 SEA FILE=REGISTRY SUB=L26 CSS FUL L30
L33 STR



VAR G1=OH/31
REP G2=(3-3) CH2
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 13
CONNECT IS M1 RC AT 17
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 12 5
NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE
L35 82 SEA FILE=REGISTRY SUB=L32 SSS FUL L33
L36 24 SEA FILE=REGISTRY ABB=ON PLU=ON L32 NOT L35
L37 22 SEA FILE=REGISTRY ABB=ON PLU=ON L36 AND (C27H42O3 OR C29H48O3 OR C28H44O3)
L38 2 SEA FILE=REGISTRY ABB=ON PLU=ON L36 NOT L37
L39 84 SEA FILE=REGISTRY ABB=ON PLU=ON (L35 OR L38)

=> d his l45-

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     (FILE 'REGISTRY' ENTERED AT 11:12:25 ON 19 DEC 2004)
               SAV L44 QAZI214E/A

     FILE 'HCAPLUS' ENTERED AT 11:24:15 ON 19 DEC 2004
L45          29 S L29
L46          20 S L44
L47          53 S L39
L48          10 S L45 AND L46 AND L47
L49          28 S L29 (L) RACT+NT/RL
L50          20 S L44 (L) RACT+NT/RL
L51          35 S L39 (L) PREP+NT/RL
L52          10 S L49 AND L50 AND L51
L53          10 S L48,L52
L54           4 S L53 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L55           1 S L54 AND (PD OR ?PALLADIUM?)
L56           4 S L54,L55
L57           4 S L56 AND L1-L8

     FILE 'REGISTRY' ENTERED AT 11:26:32 ON 19 DEC 2004

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 11:26:56 ON 19 DEC 2004
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FILE COVERS 1907 - 19 Dec 2004  VOL 141 ISS 26
FILE LAST UPDATED: 17 Dec 2004  (20041217/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d l57 all hitstr tot

L57  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   1999:271054  HCAPLUS
DN   130:296894
ED   Entered STN:  03 May 1999
TI   Preparation of vitamin D3 derivatives for the treatment of osteoporosis
IN   Takayama, Hiroaki; Konno, Katsuhiro; Maki, Shojiro
PA   Teijin Ltd., Japan
SO   Jpn. Kokai Tokkyo Koho, 24 pp.
     CODEN: JKXXAF
DT   Patent
LA   Japanese
IC   ICM  C07C401-00
     ICS  C07C029-40; C07C033-048; C07F007-18; A61K031-59; C07B061-00
CC   32-7 (Steroids)
     Section cross-reference(s): 1
FAN.CNT 2
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI	JP 11116551	A2	19990427	JP 1998-160647	19970502 <--
PRAI	JP 1996-235144	A	19960905 <--		
	JP 1996-314693	A	19961126 <--		
	JP 1997-114695	A3	19970502 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
JP 11116551	ICM	C07C401-00
	ICS	C07C029-40; C07C033-048; C07F007-18; A61K031-59; C07B061-00

OS MARPAT 130:296894

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 1,25-Dihydroxy-2-methylvitamin D3 derivs. of formula I [R1, R2 = H, alkyl] are prepared for the treatment of osteoporosis. Thus, III was added to IV, then deprotected to give II. The vitamin D receptor affinity of II was 400, compared to 100 for 1α,25-dihydroxyvitamin D3.

ST vitamin D3 deriv prepn vitamin D receptor; osteoporosis vitamin D3 deriv prepn

IT Vitamin D receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

IT Osteoporosis
(therapeutic agents; preparation of vitamin D3 derivs. for the treatment of osteoporosis)

IT **158388-11-5P 203126-73-2P 203126-91-4P**
203126-92-5P 203126-93-6P 203126-94-7P
203126-95-8P 203126-96-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

IT 1066-54-2, Ethynyltrimethylsilane 20445-33-4, (S)-MTPA-Cl 39637-99-5, (R)-MTPA-Cl 80657-57-4 **143705-63-9**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

IT 92817-88-4P 95514-03-7P 95514-04-8P 132117-93-2P
203126-90-3P 215394-09-5P 215394-10-8P
215394-12-0P 215394-15-3P 215394-17-5P
215394-20-0P 215394-22-2P 215394-23-3P
215394-24-4P 215394-34-6P 215394-35-7P 215394-36-8P
223437-33-0P 223437-37-4P 223437-39-6P 223437-51-2P
223437-60-3P
RL: **RCT (Reactant)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

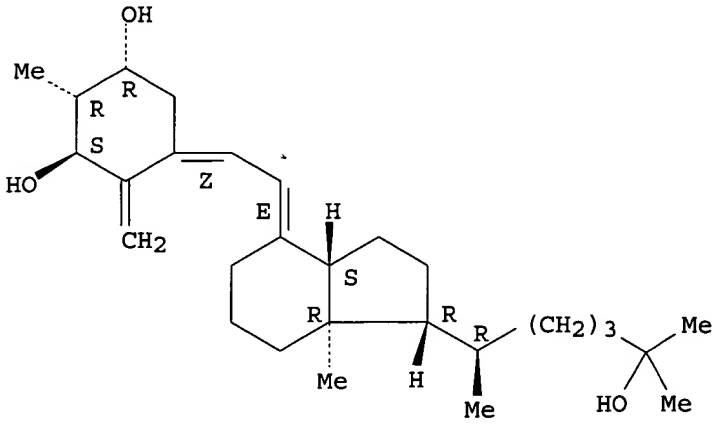
IT 215394-37-9P 215394-38-0P 223437-41-0P 223437-43-2P 223437-46-5P 223437-49-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

IT **158388-11-5P 203126-73-2P 203126-91-4P**
203126-92-5P 203126-93-6P 203126-94-7P
203126-95-8P 203126-96-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU

(Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

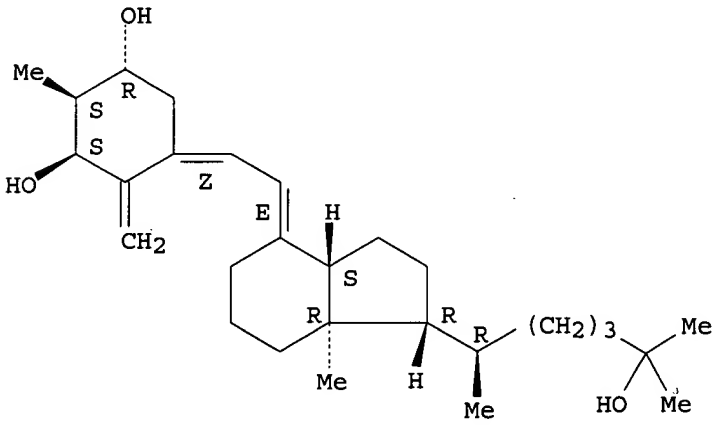
RN 158388-11-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



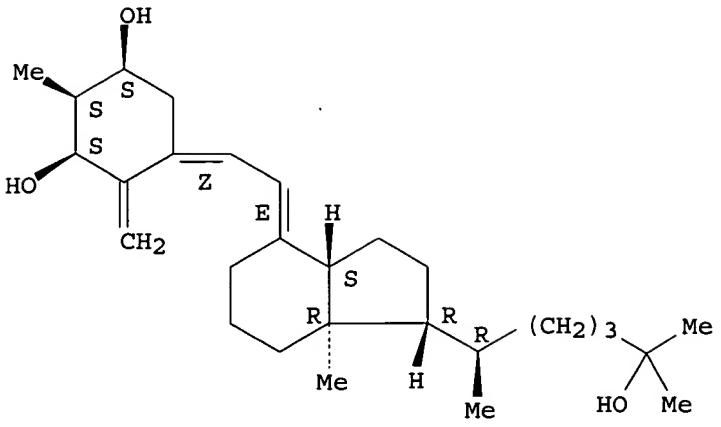
RN 203126-73-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



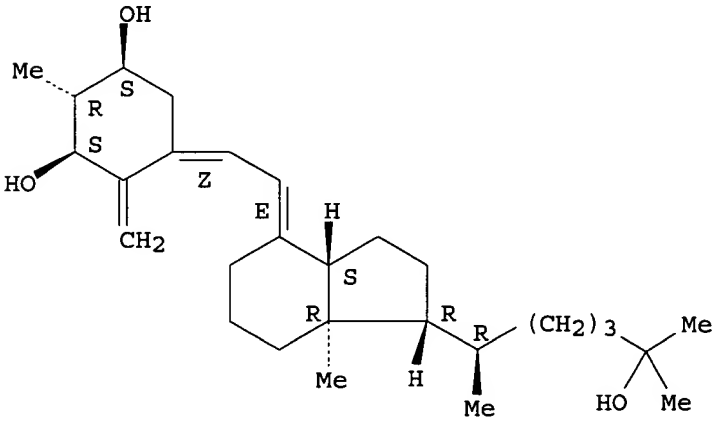
RN 203126-91-4 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2α,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



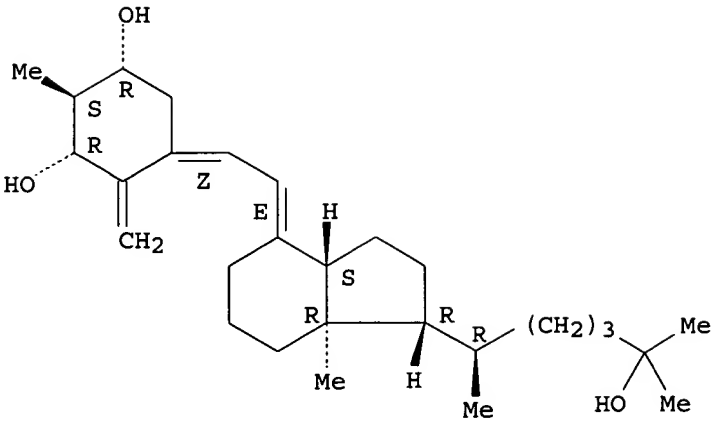
RN 203126-92-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



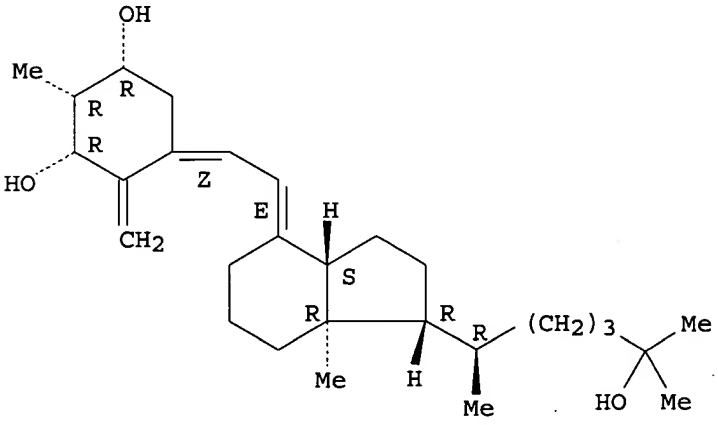
RN 203126-93-6 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



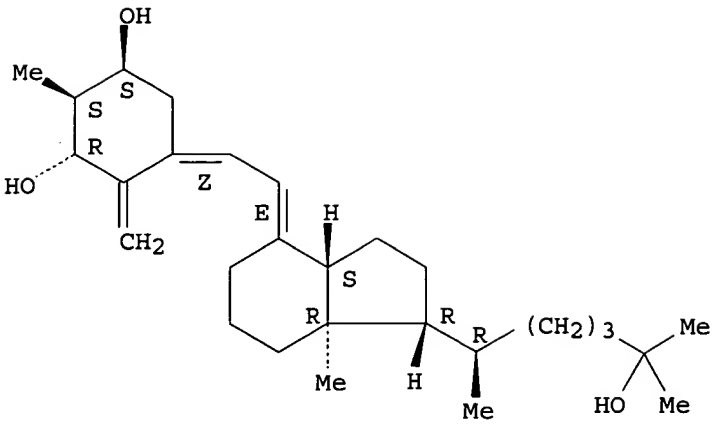
RN 203126-94-7 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



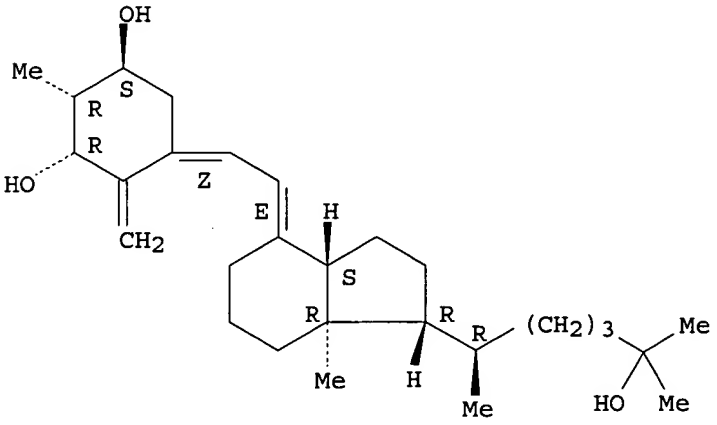
RN 203126-95-8 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



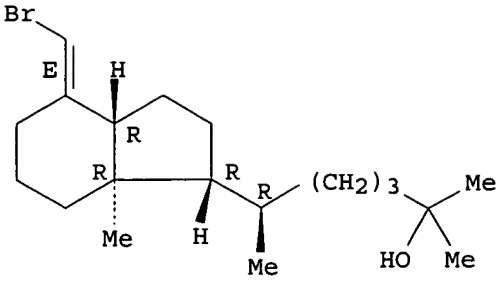
RN 203126-96-9 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



IT **143705-63-9**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)
RN 143705-63-9 HCAPLUS
CN 1H-Indene-1-pentanol, 4-(bromomethylene)octahydro-α,α,ε,7a-tetramethyl-, (εR,1R,3aR,4E,7aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

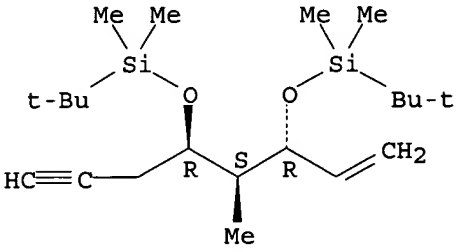


IT **203126-90-3P 215394-09-5P 215394-10-8P**
215394-12-0P 215394-15-3P 215394-17-5P
215394-20-0P 215394-22-2P 215394-23-3P
215394-24-4P 223437-60-3P
RL: **RCT (Reactant)**; **SPN (Synthetic preparation)**;
PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. for the treatment of osteoporosis)

RN 203126-90-3 HCAPLUS

CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6S,7R)- (9CI) (CA INDEX NAME)

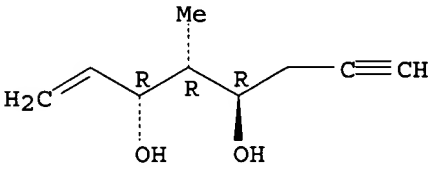
Absolute stereochemistry. Rotation (+).



RN 215394-09-5 HCAPLUS

CN 1-Octen-7-yne-3,5-diol, 4-methyl-, (3R,4R,5R)- (9CI) (CA INDEX NAME)

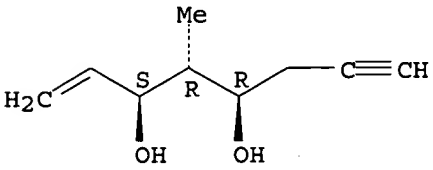
Absolute stereochemistry. Rotation (-).



RN 215394-10-8 HCAPLUS

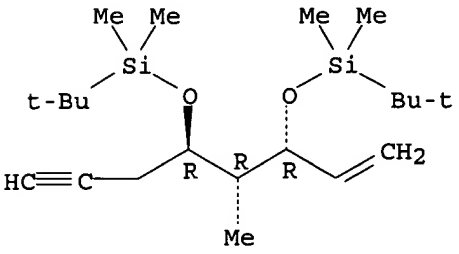
CN 1-Octen-7-yne-3,5-diol, 4-methyl-, (3S,4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



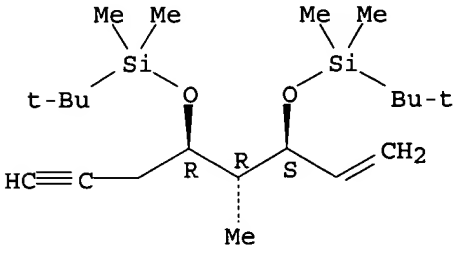
RN 215394-12-0 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



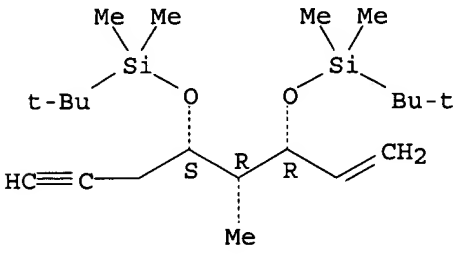
RN 215394-15-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



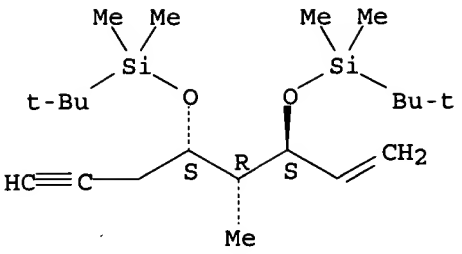
RN 215394-17-5 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6R,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



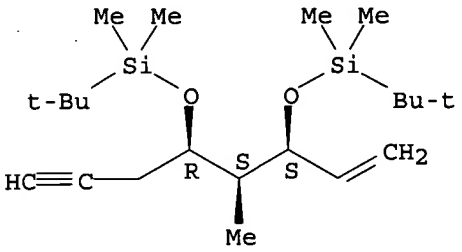
RN 215394-20-0 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6R,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



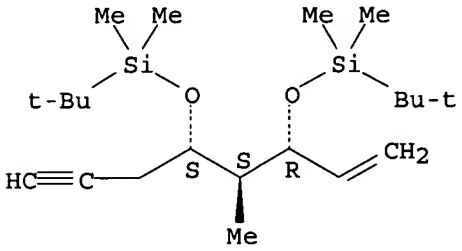
RN 215394-22-2 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6S,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



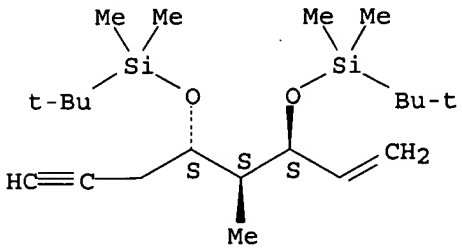
RN 215394-23-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6S,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



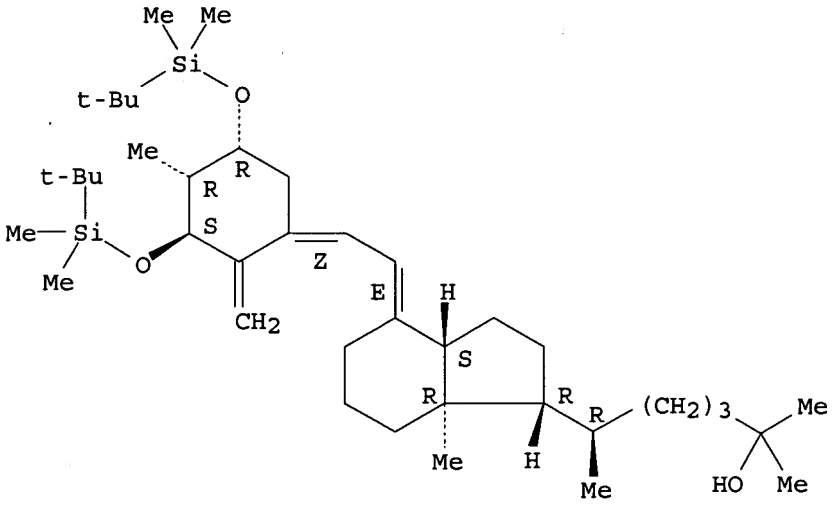
RN 215394-24-4 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6S,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 223437-60-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-25-ol, 1,3-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-, (1α,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L57 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:745027 HCAPLUS
DN 129:343629
ED Entered STN: 24 Nov 1998
TI Preparation of vitamin D3 derivatives and their pharmaceutical uses
IN **Takayama, Hiroaki; Konno, Katsuhiro; Fujishima, Toshie**
PA **Teijin Ltd., Japan**
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07C401-00
ICS A61K031-59
CC 32-7 (Steroids)
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9850353	A1	19981112	WO 1998-JP1979	19980430	<--
	W: JP, US					
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	EP 957088	A1	19991117	EP 1998-917742	19980430	<--
	EP 957088	B1	20021218			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	AT 229937	E	20030115	AT 1998-917742	19980430	<--
PRAI	JP 1997-114695	A	19970502	<--		
	WO 1998-JP1979	W	19980430	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9850353	ICM	C07C401-00

ICS A61K031-59
WO 9850353 ECLA A61K031/59 <--
OS CASREACT 129:343629; MARPAT 129:343629
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 1,25-Dihydroxy-2-Me vitamin D3 derivs. I [R1, R2 = H, tri(C1-7alkyl)silyl; the asym. carbon atoms at the 1-, 2- and 3-positions each independently has an α- or β-configuration], useful as remedies for osteoporosis, rachitis, accessory thyroidal hyperenergia, etc., are prepared via reaction of II (X = bromo, iodo) with III (R3, R4 = H, trihydrocarbylsilyl) in the presence of a **palladium** catalyst optionally followed by deprotection (removal of silyl groups). Thus, II (X = Br) was reacted with III (R3 = R4 = TBS) in toluene containing Et3N, Pd2(dba)3.CHCl3, and Ph3P at 120° to give IV (R = TBS), which was treated with camphor-10-sulfonic acid in methanol to give 63% IV (R = H). In a study using 1α,25-dihydroxyvitamin D3 receptors in the bovine thymus gland, this showed an affinity of 160 compared with 100 for 1α,25-dihydroxyvitamin D3.

ST vitamin D3 deriv prepn biol use; osteoporosis therapy vitamin D3 deriv prepn; rachitis therapy vitamin D3 deriv prepn; thyroidal hyperenergia therapy vitamin D3 deriv

IT Thyroid gland, disease
(hyperengergia; preparation of vitamin D3 derivs. and their pharmaceutical uses)

IT Rickets
(preparation of vitamin D3 derivs. and their pharmaceutical uses)

IT Osteoporosis
(therapeutic agents; preparation of vitamin D3 derivs. and their pharmaceutical uses)

IT **158388-11-5P 214351-93-6P 214351-94-7P**
214351-95-8P 214351-96-9P 214351-97-0P
214351-98-1P 214351-99-2P 215394-65-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of vitamin D3 derivs. and their pharmaceutical uses)

IT 52522-40-4
RL: CAT (Catalyst use); USES (Uses)
(preparation of vitamin D3 derivs. and their pharmaceutical uses)

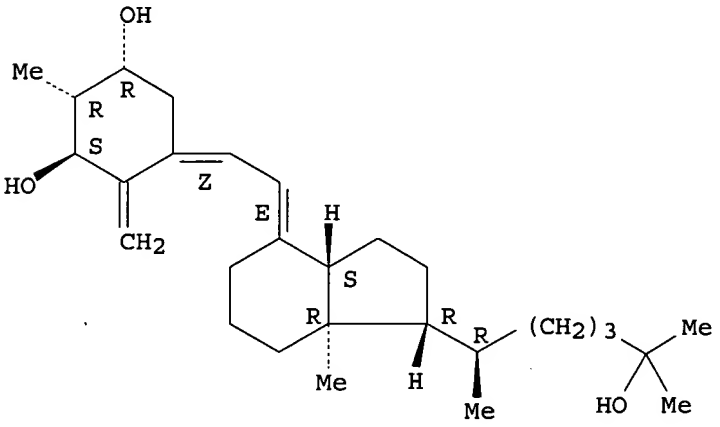
IT 67-64-1, 2-Propanone, reactions 1066-54-2, Ethynyltrimethylsilane 18162-48-6, tert-Butyldimethylsilyl chloride 20445-33-4 39637-99-5 69739-34-0, tert-Butyldimethylsilyl triflate **143705-63-9**
214351-89-0
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. and their pharmaceutical uses)

IT 104701-87-3P 112057-64-4P 147915-53-5P 147915-54-6P
203126-90-3P 215394-09-5P 215394-10-8P
215394-12-0P 215394-15-3P 215394-17-5P
215394-20-0P 215394-22-2P 215394-23-3P
215394-24-4P 215394-25-5P 215394-26-6P 215394-27-7P
215394-28-8P 215394-29-9P 215394-30-2P 215394-31-3P 215394-32-4P
215394-33-5P 215394-34-6P 215394-35-7P 215394-36-8P 215394-37-9P
215394-38-0P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. and their pharmaceutical uses)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

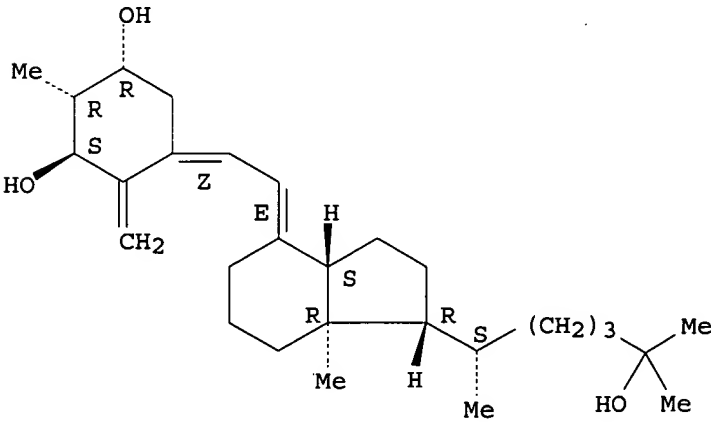
RE
(1) Chugai Pharmaceutical Co Ltd; JP 06-41059 A 1994 HCAPLUS
(2) Nayeri, S; J Cell Biochem 1996, V62(3), P325 HCAPLUS
IT **158388-11-5P 214351-93-6P 214351-94-7P**
214351-95-8P 214351-96-9P 214351-97-0P
214351-98-1P 214351-99-2P 215394-65-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of vitamin D3 derivs. and their pharmaceutical uses)
RN 158388-11-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



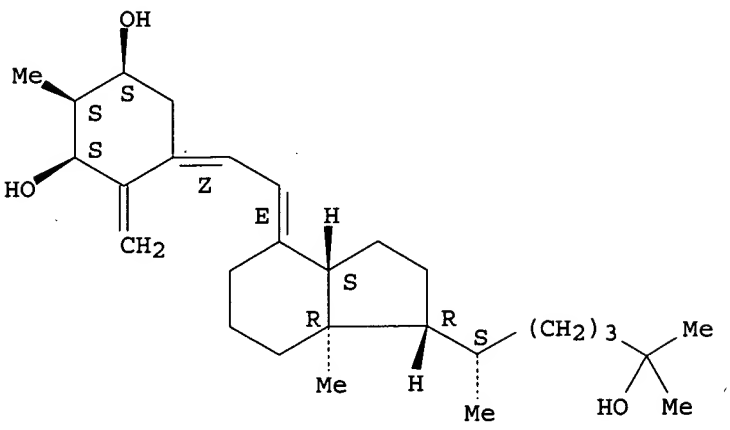
RN 214351-93-6 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



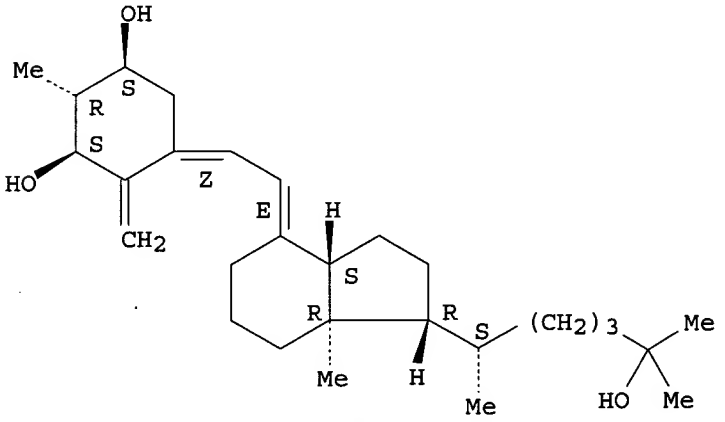
RN 214351-94-7 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2α,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



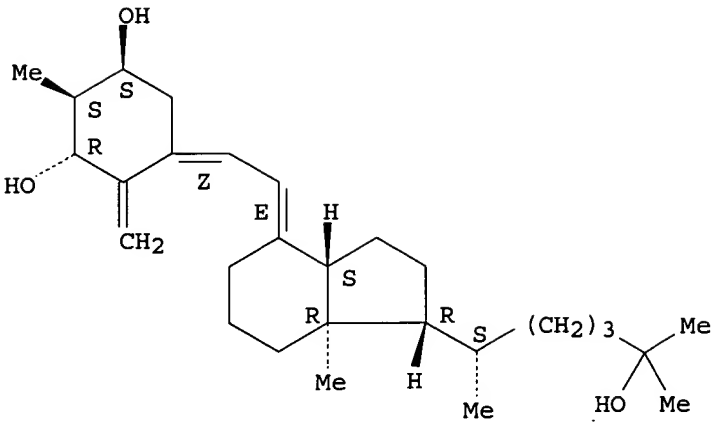
RN 214351-95-8 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



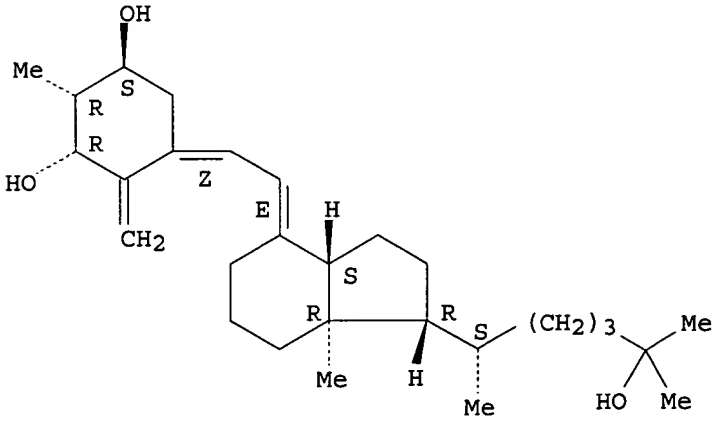
RN 214351-96-9 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



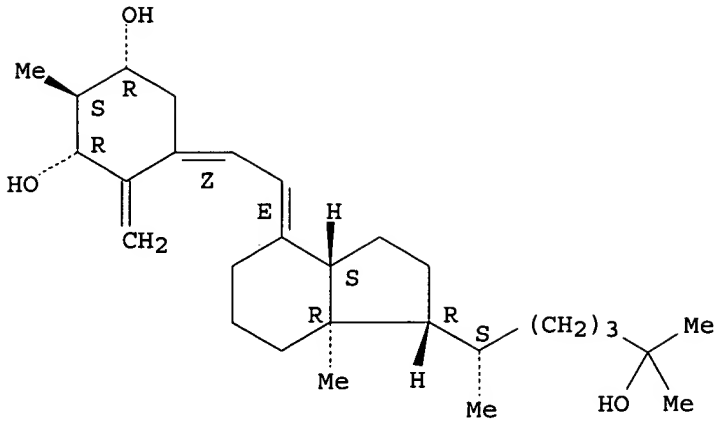
RN 214351-97-0 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



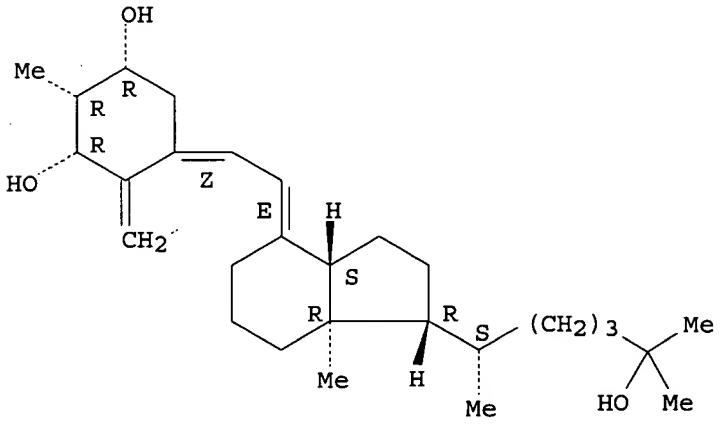
RN 214351-98-1 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



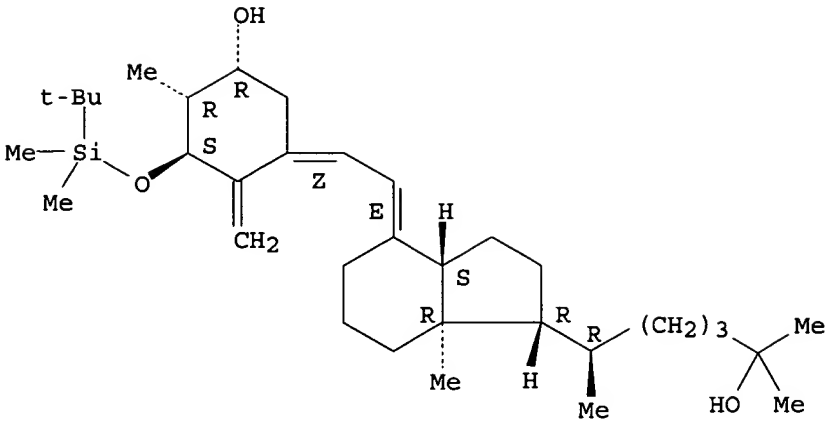
RN 214351-99-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



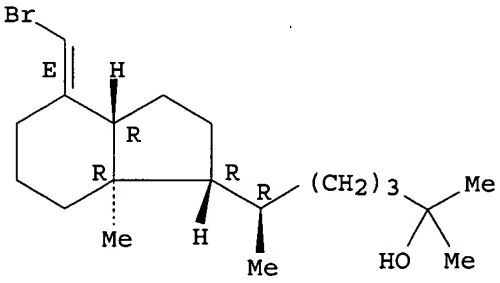
RN 215394-65-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-3,25-triol, 1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-, (1α,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



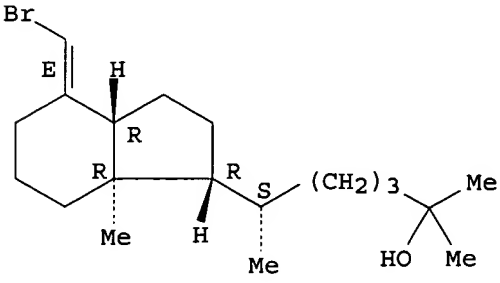
IT **143705-63-9 214351-89-0**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. and their pharmaceutical uses)
RN 143705-63-9 HCAPLUS
CN 1H-Indene-1-pentanol, 4-(bromomethylene)octahydro-α,α,ε,7a-tetramethyl-, (εR,1R,3aR,4E,7aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 214351-89-0 HCAPLUS
CN 1H-Indene-1-pentanol, 4-(bromomethylene)octahydro-α,α,ε,7a-tetramethyl-, (εS,1R,3aR,4E,7aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

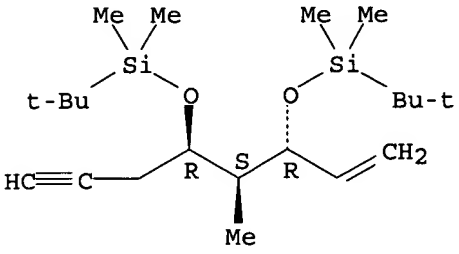


IT **203126-90-3P 215394-09-5P 215394-10-8P**
215394-12-0P 215394-15-3P 215394-17-5P

215394-20-0P 215394-22-2P 215394-23-3P
215394-24-4P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of vitamin D3 derivs. and their pharmaceutical uses)

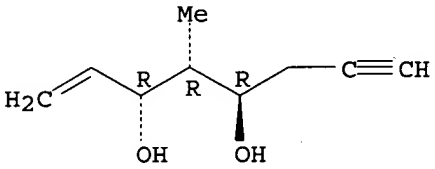
RN 203126-90-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6S,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



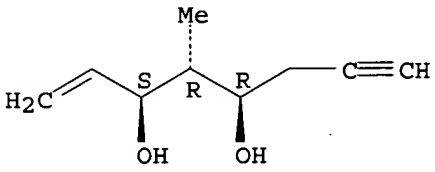
RN 215394-09-5 HCAPLUS
CN 1-Octen-7-yne-3,5-diol, 4-methyl-, (3R,4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



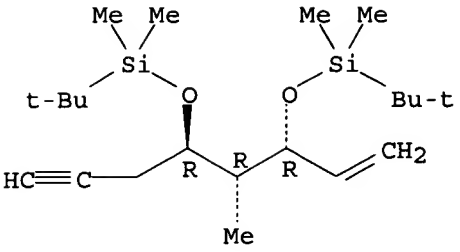
RN 215394-10-8 HCAPLUS
CN 1-Octen-7-yne-3,5-diol, 4-methyl-, (3S,4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



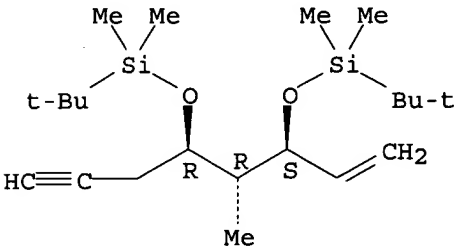
RN 215394-12-0 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



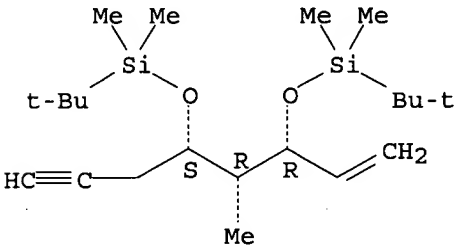
RN 215394-15-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



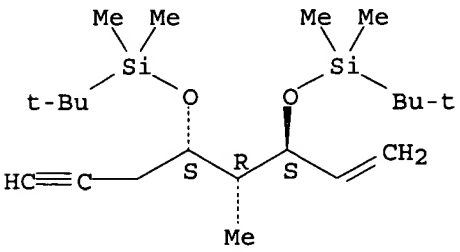
RN 215394-17-5 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6R,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



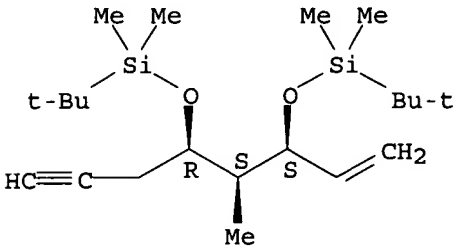
RN 215394-20-0 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6R,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



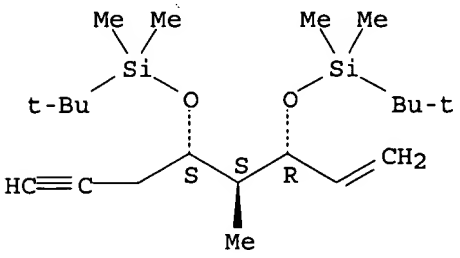
RN 215394-22-2 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6S,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



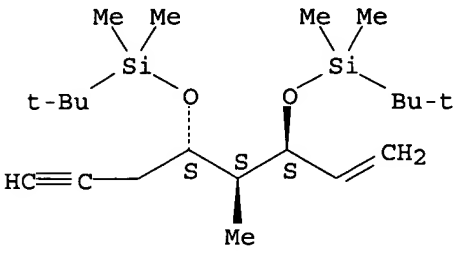
RN 215394-23-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6S,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 215394-24-4 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5S,6S,7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L57 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:606883 HCAPLUS
DN 129:290279
ED Entered STN: 25 Sep 1998
TI Synthesis and biological activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3
AU **Fujishima, Toshie**; Liu, Zhaopeng; Miura, Daishiro; Chokki, Manabu; Ishizuka, Seiichi; **Konno, Katsuhiro**; **Takayama, Hiroaki**
CS Faculty of Pharmaceutical Sciences, Teikyo University, Kanagawa, 199-0195, Japan

SO Bioorganic & Medicinal Chemistry Letters (**1998**), 8(16), 2145-2148
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 32-7 (Steroids)
Section cross-reference(s): 1

AB Synthesis and biol. evaluation of all eight possible A-ring diastereomers of 2-methyl-20-epi-1,25-dihydroxyvitamin D3 are described. Among the analogs synthesized, 2α-methyl-20-epi-1α,25-dihydroxyvitamin D3 exhibited exceptionally high potency. The double modification of 2-Me substitution and 20-epimerization yielded analogs with unique activity profiles.

ST dihydroxyvitamin D3 analogs prepn; receptor binding cell differentiation calcium mobilization

IT Cell differentiation
(HL-60; synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vitamin D binding; synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

IT 32222-06-3P, 1α,25-Dihydroxyvitamin D3
RL: PNU (Preparation, unclassified); PREP (Preparation)
(Synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

IT **214351-84-5P 214351-93-6P 214351-94-7P**
214351-95-8P 214351-96-9P 214351-97-0P
214351-98-1P 214351-99-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

IT 104651-47-0 **203126-90-3** 214351-87-8
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

IT 171011-48-6P 183506-75-4P 213250-67-0P 214351-86-7P 214351-88-9P
214351-89-0P 214351-91-4P 214351-92-5P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
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(5) Ettinger, R; Adv Drug Res 1996, V28, P269 HCAPLUS
(6) Fernandez, B; J Org Chem 1992, V57, P3173 HCAPLUS
(7) Honda, A; Steroids 1991, V56, P142 HCAPLUS
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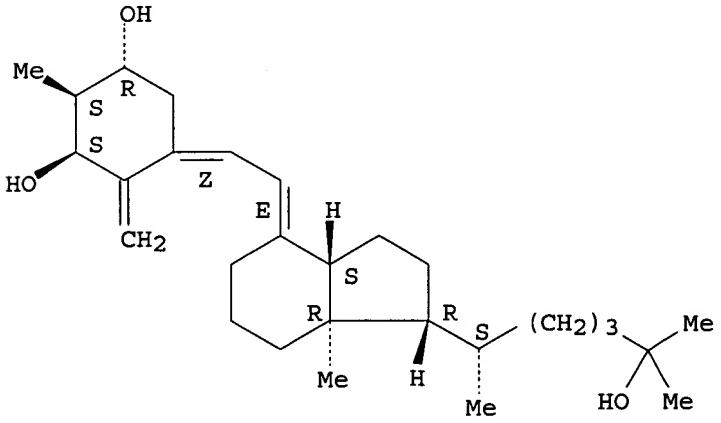
(14) Trost, B; J Am Chem Soc 1992, V114, P9836 HCAPLUS
(15) Wing, R; J Am Chem Soc 1975, V97, P4980 HCAPLUS

IT **214351-84-5P 214351-93-6P 214351-94-7P**
214351-95-8P 214351-96-9P 214351-97-0P
214351-98-1P 214351-99-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)

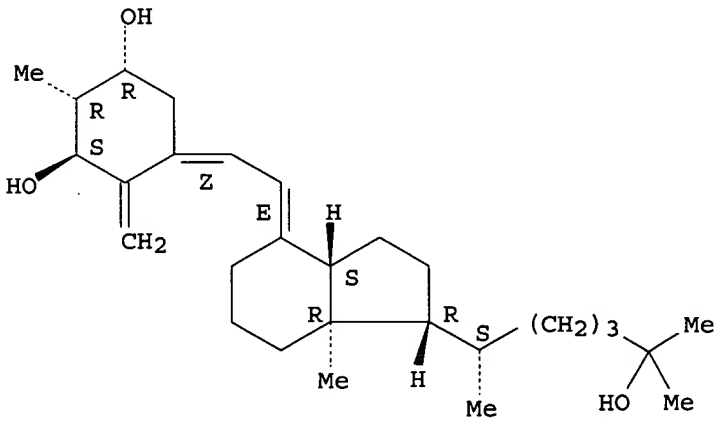
RN 214351-84-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2α,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 214351-93-6 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

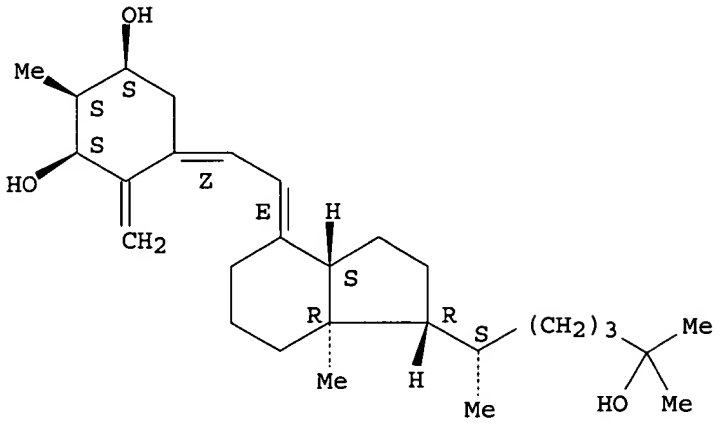
Absolute stereochemistry.
Double bond geometry as shown.



RN 214351-94-7 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-,

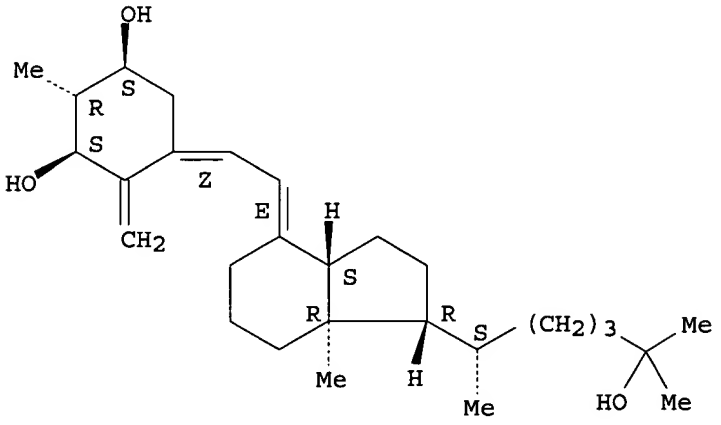
(1α,2α,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



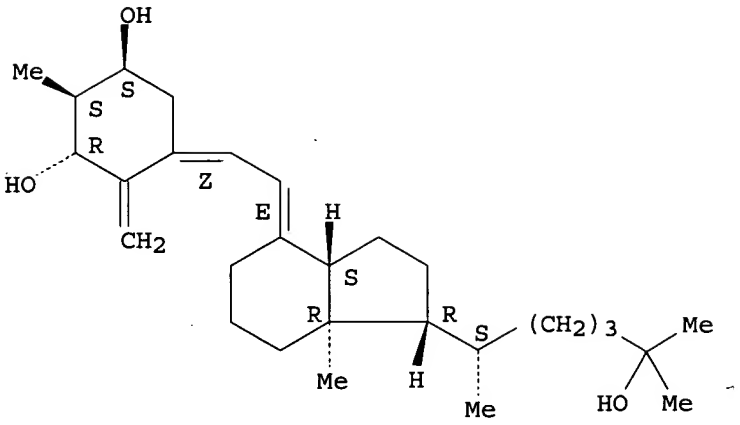
RN 214351-95-8 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



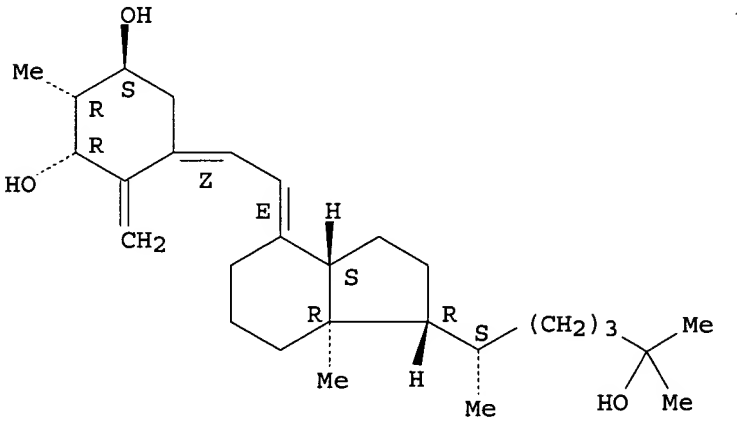
RN 214351-96-9 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



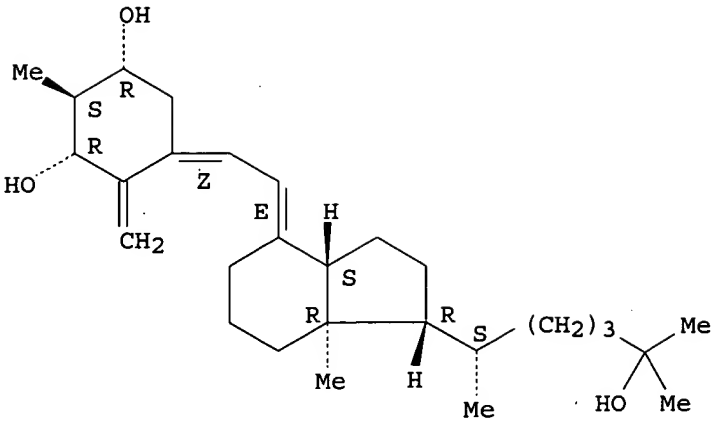
RN 214351-97-0 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3α,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



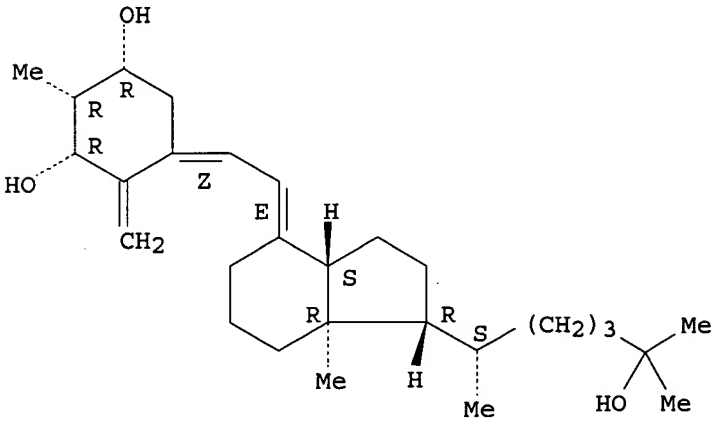
RN 214351-98-1 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



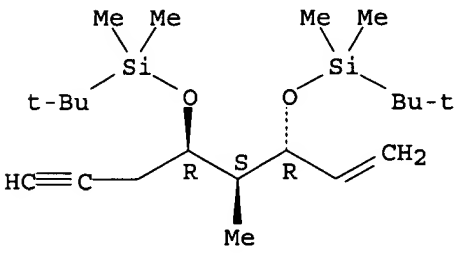
RN 214351-99-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



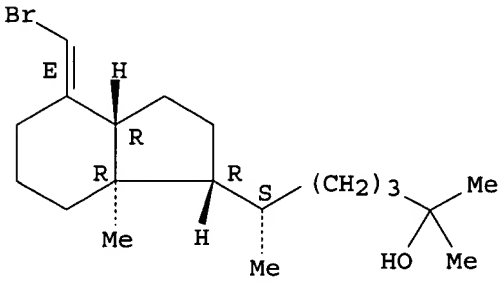
IT **203126-90-3**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)
RN 203126-90-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6S,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

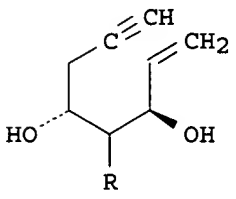


IT **214351-89-0P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(synthesis and biol. activity of 2-methyl-20-epi analogs of 1α,25-dihydroxyvitamin D3)
RN 214351-89-0 HCAPLUS
CN 1H-Indene-1-pentanol, 4-(bromomethylene)octahydro-α,α,ε,7a-tetramethyl-, (εS,1R,3aR,4E,7aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L57 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:85846 HCAPLUS
DN 128:180577
ED Entered STN: 14 Feb 1998
TI A novel and practical route to A-ring enyne synthon for 1α,25-dihydroxyvitamin D3 analogs: synthesis of A-ring diastereomers of 1α,25-dihydroxyvitamin D3 and 2-methyl-1,25-dihydroxyvitamin D3
AU **Konno, Katsuhiro**; Maki, Shojiro; **Fujishima, Toshie**; Liu, Zhaopeng; Miura, Daishiro; Chokki, Manabu; **Takayama, Hiroaki**
CS Faculty Pharmaceutical Sciences, Teikyo Univ., Sagamiko, Kanagawa, 199-01, Japan
SO Bioorganic & Medicinal Chemistry Letters (**1998**), 8(2), 151-156
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 32-7 (Steroids)
Section cross-reference(s): 2
OS CASREACT 128:180577
GI



II

AB A novel and practical route to the A-ring enyne synthon II (R = H, Me), which can be versatile for a variety of A-ring analogs of 1α,25-dihydroxyvitamin D3 (I), was developed. This novel method led to an improved synthesis of the A-ring diastereomers of I, and synthesis of the new analogs, 2-methyl-1,25-dihydroxyvitamin D3 with its all

possible diastereomers. The biol. evaluation of the 2-Me analogs showed the ααβ-isomer to be more potent than I.

ST A ring enyne vitamin D synthon

IT Synthons
(chiral; preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

IT Vitamin D receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

IT Alkenynes
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

IT 32222-06-3DP, 1α,25-Dihydroxyvitamin D3, A-ring analogs
158388-11-5P 203126-73-2P 203126-91-4P
203126-92-5P 203126-93-6P 203126-94-7P
203126-95-8P 203126-96-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

IT 2653-90-9 72657-23-9, Methyl (R)-3-hydroxy-2-methylpropionate
80657-57-4, Methyl (S)-3-hydroxy-2-methylpropionate **143705-63-9**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

IT 152032-72-9P 161055-41-0P 169310-79-6P 169315-01-9P 203126-72-1P
203126-74-3P 203126-76-5P 203126-78-7P 203126-79-8P 203126-80-1P
203126-81-2P 203126-83-4P 203126-84-5P 203126-85-6P 203126-86-7P
203126-87-8P 203126-88-9P **203126-89-0P 203126-90-3P**
203126-97-0P 203126-98-1P 203126-99-2P 203127-00-8P 203127-01-9P
203127-02-0P 203127-03-1P **203127-04-2P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

IT 61476-45-7P 66791-71-7P 96614-28-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Bouillon, R; Endocri Rev 1995, V16, P200 HCAPLUS
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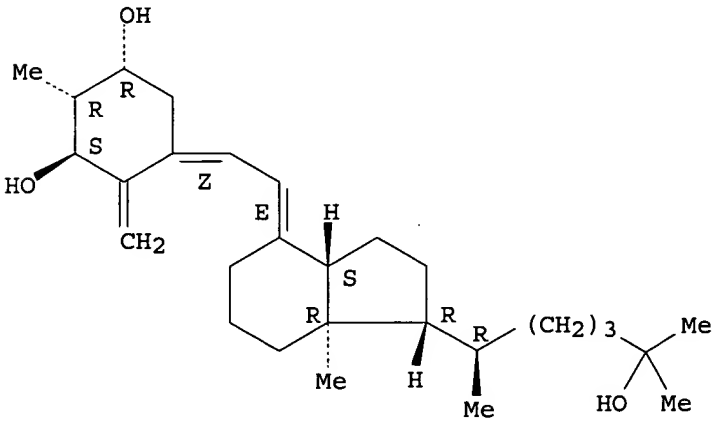
(23) Trost, B; J Am Chem Soc 1992, V114, P9836 HCAPLUS
(24) Trost, B; Tetrahedron Lett 1994, V35, P8119 HCAPLUS
(25) Vrielynck, S; Tetrahedron Lett 1995, V36, P9023 HCAPLUS
(26) Wing, R; J Am Chem Soc 1975, V97, P4980 HCAPLUS
(27) Zhu, G; Chem Rev 1995, V95, P1877 HCAPLUS

IT **158388-11-5P 203126-73-2P 203126-91-4P 203126-92-5P 203126-93-6P 203126-94-7P 203126-95-8P 203126-96-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **SPN (Synthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)

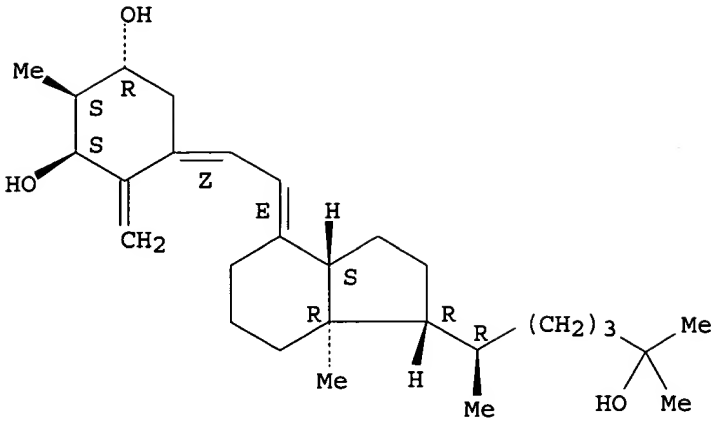
RN 158388-11-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



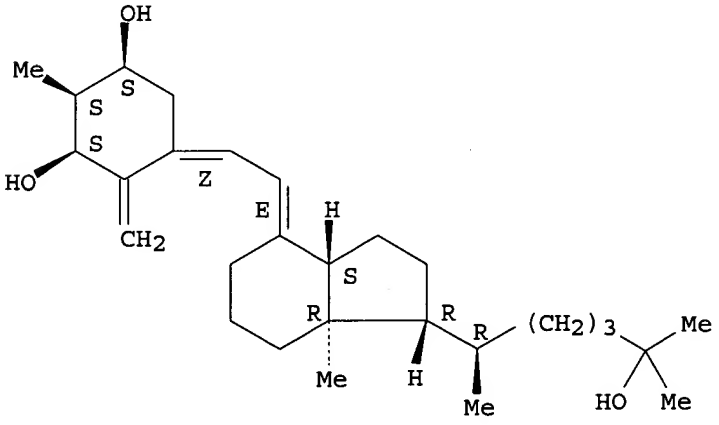
RN 203126-73-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



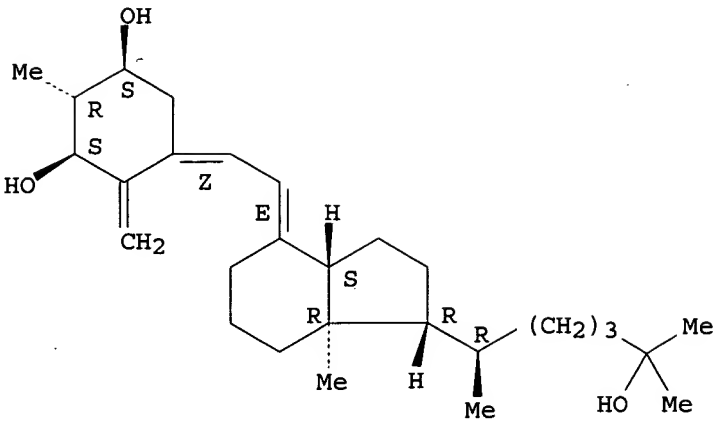
RN 203126-91-4 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2α,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



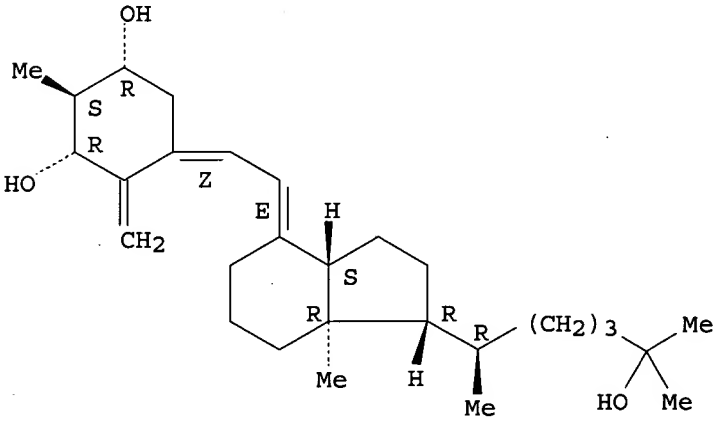
RN 203126-92-5 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1α,2β,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



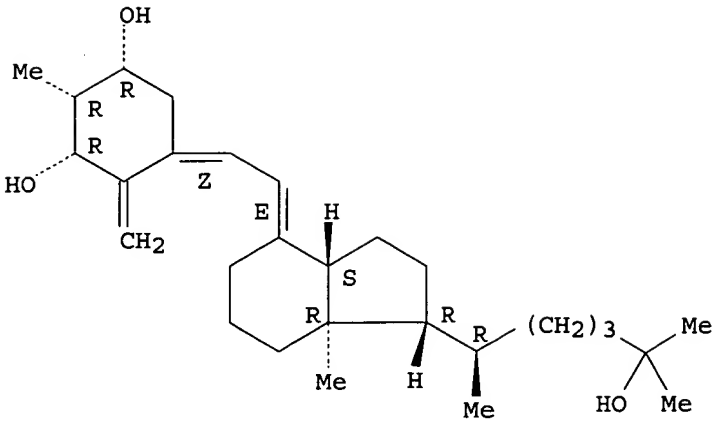
RN 203126-93-6 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



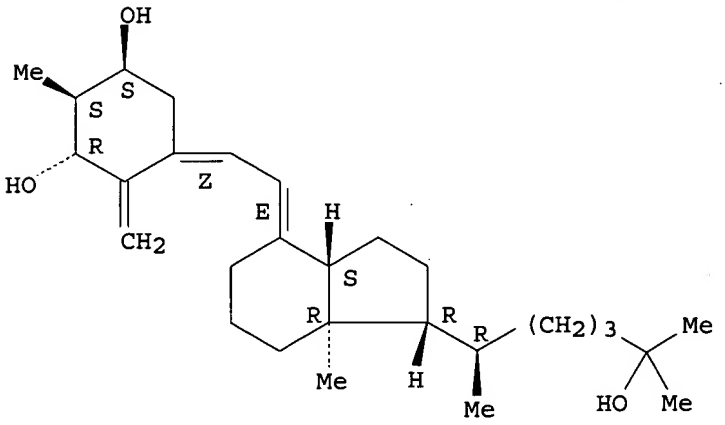
RN 203126-94-7 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



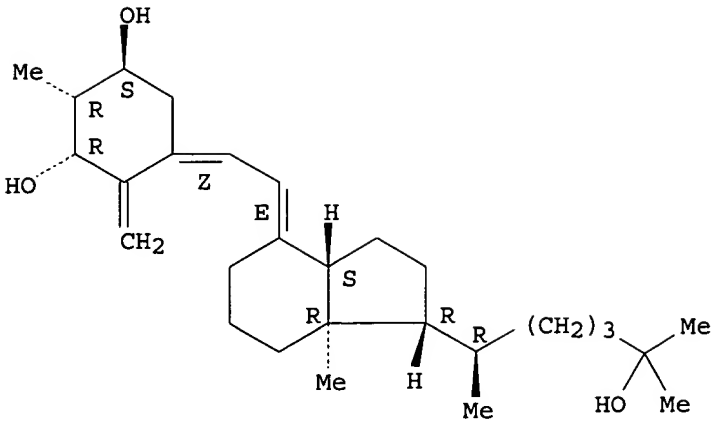
RN 203126-95-8 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2α,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



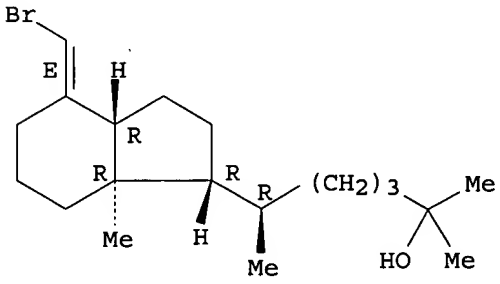
RN 203126-96-9 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 2-methyl-, (1β,2β,3α,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



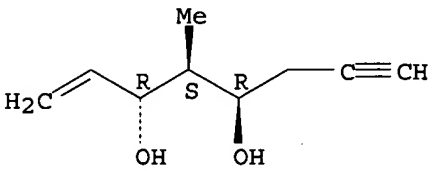
IT **143705-63-9**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)
RN 143705-63-9 HCAPLUS
CN 1H-Indene-1-pentanol, 4-(bromomethylene)octahydro-α,α,ε,7a-tetramethyl-, (εR,1R,3aR,4E,7aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



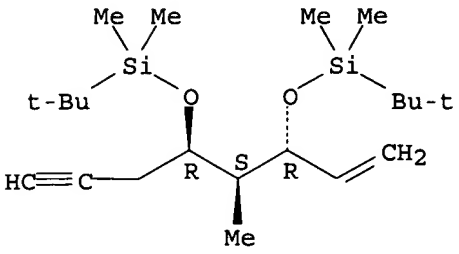
IT **203126-89-0P 203126-90-3P 203127-04-2P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(preparation of A-ring enyne synthons and 1α,25-dihydroxyvitamin D3 analogs)
RN 203126-89-0 HCAPLUS
CN 1-Octen-7-yne-3,5-diol, 4-methyl-, (3R,4S,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



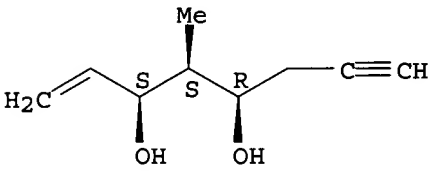
RN 203126-90-3 HCAPLUS
CN 4,8-Dioxa-3,9-disilaundecane, 5-ethenyl-2,2,3,3,6,9,9,10,10-nonamethyl-7-(2-propynyl)-, (5R,6S,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 203127-04-2 HCAPLUS
CN 1-Octen-7-yne-3,5-diol, 4-methyl-, (3S,4S,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> d his

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     (FILE 'HOME' ENTERED AT 10:56:35 ON 19 DEC 2004)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 10:56:52 ON 19 DEC 2004
L1             2 S (WO98-JP1979 OR JP97-114695)/AP,PRN
               E TEIJIN/PA,CS
               E TEIJI/PA,CS
L2         20333 S E3-E12 OR TEIJIN?/PA,CS
               E TAKAYAMA H/AU
L3            98 S E3
               E TAKAYAMA HIRO/AU
L4           206 S E4
               E KONNO K/AU
L5           223 S E3,E7
               E FUJISHIMA T/AU
L6            13 S E3
               E FUJISHIMA TOSHI/AU
L7            42 S E4
               E HIROAKI T/AU
L8             4 S E3
               E KATSUHIRO K/AU
               E TOSHIE F/AU
               SEL RN L1

     FILE 'REGISTRY' ENTERED AT 10:59:21 ON 19 DEC 2004
L9            67 S E1-E67
L10           24 S L9 AND NR>=3
L11           17 S L10 AND C5-C6/ES AND C6/ES
L12           43 S L9 NOT L10

     FILE 'CASREACT' ENTERED AT 11:03:46 ON 19 DEC 2004
L13               STR
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L14            0 S L13
L15              STR L13
L16            0 S L15
L17              STR L15
L18            0 S L17
L19            8 S L17 FUL
                 SAV L19 QAZI214/A
L20            1 S L19 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L21            8 S L19 AND (TEIJIN?/PA,CS OR (TAKAYAMA ? OR KONNO ? OR FUJISHIMA
L22            1 S L20 AND L21
L23            7 S L21 NOT L22

     FILE 'CASREACT' ENTERED AT 11:10:45 ON 19 DEC 2004

     FILE 'REGISTRY' ENTERED AT 11:12:25 ON 19 DEC 2004
L24              STR
L25             50 S L24 CSS SAM
L26           1136 S L24 CSS FUL
                 SAV L26 QAZI214A/A
L27              STR L24
L28            0 S L27 CSS SAM SUB=L26
L29            4 S L27 CSS FUL SUB=L26
                 SAV L29 QAZI214B/A
L30              STR L24
L31            8 S L30 CSS SAM SUB=L26
L32          106 S L30 CSS FUL SUB=L26
                 SAV L32 QAZI214C/A
L33              STR L30
L34            7 S L33 SAM SUB=L32
L35           82 S L33 FUL SUB=L32
                 SAV L35 QAZI214D/A
L36           24 S L32 NOT L35
L37           22 S L36 AND (C27H42O3 OR C29H48O3 OR C28H44O3)
L38            2 S L36 NOT L37
L39           84 S L35,L38
L40              STR
L41            3 S L40 CSS
L42              STR L40
L43            2 S L42 CSS SAM
L44           23 S L42 CSS FUL
                 SAV L44 QAZI214E/A

     FILE 'HCAPLUS' ENTERED AT 11:24:15 ON 19 DEC 2004
L45           29 S L29
L46           20 S L44
L47           53 S L39
L48           10 S L45 AND L46 AND L47
L49           28 S L29 (L) RACT+NT/RL
L50           20 S L44 (L) RACT+NT/RL
L51           35 S L39 (L) PREP+NT/RL
L52           10 S L49 AND L50 AND L51
L53           10 S L48,L52
L54            4 S L53 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L55            1 S L54 AND (PD OR ?PALLADIUM?)
L56            4 S L54,L55
L57            4 S L56 AND L1-L8

     FILE 'REGISTRY' ENTERED AT 11:26:32 ON 19 DEC 2004

     FILE 'HCAPLUS' ENTERED AT 11:26:56 ON 19 DEC 2004

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